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COLLAGEN DISEASES

LUPUS ERYTHEMATOSUS, POLYARTERITIS, SCLERODERMA, DERMATOMYOSITIS, AND THROMBOTIC THROMBOCYTOPENIC PURPURA

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GOUT

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CONTENTS

PREFACE vi
COLOR PLATES . . . ix–xvi

HISTORY 1
DEFINITION . . . 5
HEREDITY 8
GOUT IN LOWER ANIMALS . . 17
INCIDENCE . . 17
Sex, 19 Age, 19 Race, 21 Social Status, 21 Season, 22
ETIOLOGY . . 22
INTERMEDIARY METABOLISM OF URIC ACID . 28
Precursors of Uric Acid, 29 Miscible Pool and Turnover Rate of Labeled Uric Acid, 32. The Influence of Diet and Total Caloric Intake, 35
URATE CONCENTRATION IN SERUM 36
RENAL EXCHANGE OF URATES 42
PHARMACOLOGY OF ANTI-GOUT DRUGS 48
Colchicine, 48 Probenecid (Benemid), 50 Phenylbutazone (Butazolidin), 57 4-(Phenylthioethyl) 1, 2-Diphenyl 3, 5 Pyrazolidinedone, 58 Salicylates, 59 Adrenal Steroids, 59
PATHOLOGY . 60
Articular Structures, 61 Kidney Tissue, 65
PATHOGENESIS OF ACUTE SYMPTOMS . . 67
X-RAY FINDINGS . 69
CLINICAL DESCRIPTION 95
Acute Attack, 95 Intercritical Period, 101 Chronic Gout, 103
PRECIPITATING AGENTS . 103
COMPLICATIONS . 107
ASSOCIATED DISEASES . 116
DIAGNOSIS . . . 122
Ancillary Items, 123 Critical Criteria, 125 Post-Attack Criteria, 127
DIFFERENTIAL DIAGNOSIS . . . 129
PROGNOSIS 142
PREVENTION . 145
TREATMENT . 146
Intercritical or Prophylactic Period, 148 Acute Attack, 173 Surgical Treatment of Chronic Deforming Gouty Arthritis, 181.

EPILOGUE . . 184
BIBLIOGRAPHY 185
INDEX 199

PREFACE

"NOT ANY OF THE *diseases to which man is liable is a cause of greater perplexity and disappointment than Gout; yet this does not arise from the oft repeated reproach of its intractable nature It may indeed be said, with truth, that it is more curable than many, and it is certainly more amenable to relief than most diseases which fall under the cognizance of physicians The regular attacks of gout cannot be said to give more embarrassment to a medical attendant than the assaults of any other malady; and, inasmuch as they are, for the most part, quite exempt from danger, they give little solicitude for the event But it is quite otherwise with its irregular forms. In the beginning of a physician's practice especially, while he is yet unfamiliar with any but the noted and typical forms of disease, the changing and mysterious phenomena of gout, and particularly its complications with other disturbances of the system, or injuries of parts, are full of doubt and difficulty.*

"*In the earliest years of my professional life, my mind was frequently called to its consideration, to the observation of its various forms, the unravelling of its strange and confusing associations with other known forms of disease, and meditation on its cause and nature I well remember how often I was perplexed by its obscure indications, how often I was surprised to discover it lurking unsuspected in the system, disturbing the healthy functions, and how greatly the intermixture of gout swaying the symptoms of other diseases from their natural and ordinary course, puzzled and disquieted me*" Gairdner, 1854[85]

These comments, prepared a century ago, have lost none of their significance and relevancy at the present time The following pages record the results of a renewed effort to describe the usual features of gout and gouty arthritis, as well as several of the unusual features Thus, it serves as an extension as well as an elaboration of the earlier monograph The volume has been completely rewritten, an entirely new up-to-date set of figures and x-rays portrayed and color plates added Faced with the problems of reprinting or rewriting, the previous monograph out of print, and so unavailable, we chose the alternative of rewriting Possibly the subconscious desire to arouse physicians to a greater interest in the

early recognition of gouty arthritis in order to insure an early and prompt treatment of the disease may have contributed in some small measure to the decision

The clinical material studied has come largely from the Arthritis Clinic and hospitalized patients at the Buffalo General Hospital The laboratory investigations have been pursued jointly in the Research Laboratory at the University of Buffalo Chronic Disease Research Institute and in the Medical Research Laboratories of this hospital, under the direct supervision of Dr Charles Bishop Technical assistance in the Research Laboratory has been rendered by Dr Royden Rand, Mrs Ann Byers, Mrs. Sheila Parizeau and Miss Barbara Maitland The several members of the Arthritis Clinic at the Buffalo General Hospital have been particularly helpful in providing clinical material Included are Drs L Maxwell Lockie, Harold Robins, Bernard M Norcross, Salvatore LaTona, Daniel Riordan and Clyde George The excellence of the roentgenography is due to the interest of Dr Gordon Culver, of the Department of Roentgenology, and Mr William F Payne, photographer The pathologic material was made available by Dr Kornel Terplan, of the Department of Pathology Mrs Geri Kassirer and Miss Joan Manley are responsible for painstaking copying of the manuscript Mr Raymond M. Verrill, of the English Department of Nichols School was the typereader Drs Lyford and Shapiro, of Lexington, Kentucky, kindly provided permission for reproduction of figure 26

I am especially grateful to Dr Henry Thomas, of Merck Sharp & Dohme, for permission to reproduce the color figures and for the preparation of the line charts The color plates appeared originally either in issues of *Seminar* or in a brochure entitled *Gout* The originals were provided from the author's teaching file in order to illustrate articles that were prepared prior to this manuscript Because of a lack of special funds, the arrangements for reproducing them would have been impossible without the support just mentioned

Several individuals and foundations have contributed directly to the support of the research program in gout and gouty arthritis under way in the Department of Medicine at the University of Buffalo School of Medicine and the Buffalo General Hospital, from which this monograph comes I am pleased, therefore, to acknowledge

financial support from the following: Mrs Kathleen B. S Chard, Cazenovia, New York; Mr Alton Wood, Eden, New York; Mr Westley Miller, Union, New Jersey; The National Institutes of Health, Bethesda, Maryland; and the Western New York Chapter of the Arthritis and Rheumatism Foundation.

JHT

Eden, New York
January, 1957



PLATE I Subsiding acute gouty arthritis in both great toes There is considerable diffuse swelling of the left foot.



PLATE II Tophaceous deposits on the hand of a patient who had suffered from attacks of acute gouty arthritis for thirty years



PLATE III Disseminated urate deposits over the cartilages of the knee and the soft tissues The patient denied a history of repeated or prolonged attacks of acute gout in this joint

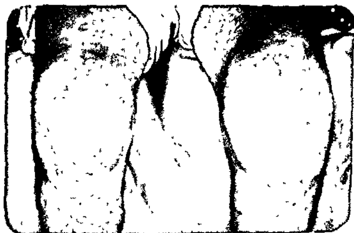


PLATE IV Extensive changes in the soft tissues of each knee were accompanied by limitation of motion. There is a large synovial effusion on the left



Plate V. Large tophi in the buttocks of a patient who suffered from severe tophaceous gout Calcium deposits were detected by x-ray in these areas, as well as urates by chemical analysis

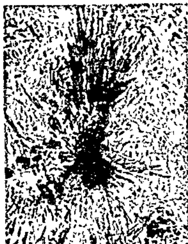


Plate VI Urate crystals in the kidney of a patient with gout



PLATE VII The kidney of a patient who had suffered from intermittent attacks of acute gouty arthritis for over twenty five years The patient died following the third myocardial infarction (See PLATE IV)



PLATE VIII. Section of a kidney shown in PLATE VII There are disseminated deposits of urate in the parenchyma and in the pelvis



PLATE IX. The foot of a patient with extensive tophaceous gout, whose toes had been amputated several years earlier. There is a large urate sinus on the lateral portion of the foot. The subcutaneous tissues are diffusely infiltrated with massive deposits of urate. (See FIG. 11.)



PLATE X. Desquamation following an acute attack of gouty arthritis of the great toe.



Plate XI A large urate tophus on the right great toe of a patient who had suffered from intermittent attacks of acute gout for more than twenty years There is a strong family history for the malady.



Plate XII Large tophaceous deposits in the olecranon bursa of a 62 year old patient who had suffered from intermittent attacks of gouty arthritis for more than twenty years



PLATE XIII Urate stones of various sizes, shapes and colors from patients with gout.



PLATE XIV. Tophi in the ear of a patient with gout

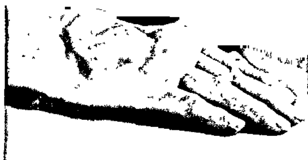


PLATE XV The hand of a patient with rheumatoid arthritis that suggested tophaceous deposits (See PLATE XVI)



PLATE XVI Tophaceous deposits in the hand of a patient with gout (See PLATE XV)

to

Mildred

my wife

History

ENDOWED WITH a bountiful and noble heritage, gout not only received recognition as a clinical entity before the birth of Christ but also has afflicted many eminent persons throughout recorded history Hippocrates,[118] 460–370 B C, was acquainted with the malady ἄβατος νόσος, the unwalkable disease Hieron of Syracuse,[63] in the fifth century B C, probably recognized this specific articular dyscrasia, for his comments on the association of joint disease and bladder stones are believed to have referred to urate calculi in patients with gouty arthritis

There are three artifacts in Egyptian archaeology worthy of note in the history of gout Smith and Jones[221] discovered a large mass in the great toe of the skeleton of an elderly male in a cemetery in Upper Egypt Urates in the deposit were identified by chemical analysis The oldest renal calculus in current collections recovered also from an Egyptian mummy who died at least 7000 years ago, contains a uric acid nucleus[138] The finding of a urate calculus does not prove that gout was responsible, although the chances are 15 to 1 in favor of such an inference A third item in Egyptian archaeology, dating from 1500 B C, is several prescriptions deciphered in the Ebers papyrus, these included crocus and saffron herbs, from which colchicum is derived Since colchicum is the only recognized specific anti-arthritis agent in ancient or modern therapeutics, it is possible that the preparations containing this active principle were used in the treatment of gouty arthritis

In 1734, Stukeley[278] called attention to two items of historical interest

"As to the history of the distemper, I need observe no more than that the earliest account we have of it is in the Scripture, and the earliest we can expect to have 'II Chron, XVI, 12 And Asa in the thirty and ninth year of his reign was diseased in his feet, until his disease was exceeding great yet in his disease he sought not to the Lord, but to the physicians And Asa slept with his fathers and died in the one and fortieth year of his reign '—It can't be doubted that this distemper was the gout —I don't suppose Asa was the first that had this distemper, but is the first recorded in history, and this is near 200 years before the foundation of Rome."

Cathedral, Cardinal Zinzendorff, Samuel Johnson, Sydenham, Louis XIV, Newton, Goethe, Gibbon, Linnaeus, Fielding, Marshall Saxe, Widal, John Hunter, Wallenstein, Condé, Wolsey, Landor, Hamilton, Charles Darwin and William Welsh, comprise indeed a unique list of afflicted. Gout was apparent in the Dukes of Lorraine for more than two centuries, from Charles II through Francois III.[155]

Hartung [111] credits a French Army officer, Nicolas Husson, with the rediscovery of colchicum in the treatment of gout, but calls him a quack. His secret preparation was labeled *eau medicinale*. Colchicum was the chief constituent of other patent medicines, including Wilson's tincture, Portland powder, Laville's tincture and Reynold's specific. Ambrose Paré used colchicum for gout in the seventeenth century.[211] In 1814, Want [284] identified colchicum as the active ingredient of the secret preparation. Six years later, Pelletier and Caventon [187] isolated the alkaloid colchicine from the meadow saffron, or *Colchicum autumnale*.

Although the whole history of the humorous treatment of gout has not been recorded, the caricatures of the malady may be traced through several generations. The cartoons of Gillray and Cruickshank on gout are collector's items.

In Gilbert and Sullivan, *The Gondoliers*, I Stole the Prince:

> "I dropped a Grand Inquisitor's tear
> That gondolier had perished
> A taste for drink, combined with gout,
> Had doubled him up forever."

Posthumus remarked in *Cymbeline*

> "Yet I am better
> Than one that's sick of the gout; since he had rather
> Groan so in perpetuity than be cur'd
> By the sure physician, death, who is the key
> To unbar these locks."

Also in the Introduction to "A Disquisition of the Stone and Gravel," etc., by S. Perry, 1785 [169]

> "To Doctors
> If this letter shall happen in any measure to spoil your trade, Heaven make me thankful. For well I know yours is the trade that have by one method or other rid out of the way, very great numbers of men. . . since your unrighteous trade is broke, or breaking, you would timely bethink yourselves

what honest employment you may be fit for Since you have presented to many a weak man a medicine for a horse, you should take to your new profession and practice on the Sparing of Gout But you must be content with less earnings What! You can't expect as much for killing a horse as a man"

The association of uric acid and gout dates from 1776, when Scheele[208] identified this substance in urine A few years later, Wollaston[273] isolated uric acid from gouty tophi In 1793, Forbes[90] extended Wollaston's observation, when he speculated that gout might be associated with an increased concentration of uric acid in the body Because of a lack of laboratory procedures for confirmation of the hypothesis at that time, Garrod[98] could not furnish convincing evidence of an increased concentration of uric acid in the blood of gouty persons until 1848 An increased concentration of uric acid was identified originally by the murexide test upon serum The famous uric acid thread test was described in 1856 The data from five gouty patients, as determined by the thread test, varied between 2 5 and 18 mg /100 ml The mean is similar to results by current biochemical methods for the determination of the constituent in the serum of gouty persons The outstanding contributions by Emil Fischer[76] revealed the derivation of purine substances Fischer also verified the structure of uric acid through its synthesis Subsequent investigations are contemporary and will be discussed in the appropriate sections

Definition

GOUT WAS CALLED podagra originally, a Greek derivation from *pous*, foot and *agra*, attack The term now in vogue has been adapted from the Latin, *gutta*, which refers to a drop as a result of "a defluxion of the humours" This broad reference is not surprising since the visible tophus is a massive precipitate of salts of uric acid Several adjectives have been employed to qualify the derivative gout or have been used in the description of the clinical syndrome and its presumed variations In spite of the persistent confusion between gout and gouty arthritis with the consequent interchangeable use of terms, this inaccuracy is not serious

Heredity

THE HEREDITARY NATURE of gout has been recognized since the earliest description of the malady. Galen,[120] Seneca,[87] and others noted the familial affiliation One of the first statistical tabulations was reported by Scudamore,[213] who computed a familial incidence of 60 per cent in his series of 522 patients Garrod[80] found the ancestral trait to be almost 80 per cent and shrewdly noted that "breed is stronger than pasture" Granville,[96] Hutchinson,[125] Luff[157] and Weil[262] also gave considerable attention to this aspect of the disease prior to the contemporary studies The familial incidence of gout in the Arthritis Clinic at the Buffalo General Hospital is more than 50 per cent in families with two or more male members Although a few references in the literature of the subject discount the familial aspects and even record values as low as 11 per cent,[35] these discrepancies may be explained by a lack of diligence in pursuing the geneologic data A positive family history may be denied if hereditary data are sought as a routine question only, in the clinical history The greater the interest of the physician, the higher the percentage of positive family histories (FIG 1). The following résumés are illustrative

A lawyer, 57 years of age, was admitted to the hospital because of "acute infectious arthritis" of the left elbow Gout was considered in the differential diagnosis and supported by the increased concentration of uric acid in the serum The values ranged from 6.8 to 7.4 mg./100 ml The response to a full course of colchicine was dramatic Not only was a family history of gout denied during the preliminaries but also the implications were resented by the patient The matter was not neglected, however, and following a specific charge to the patient to pursue the possibility, the results were positive At a family reunion some time later, the patient obtained the information that a paternal uncle had suffered severely from gouty arthritis in the later years of his life

A salesman, seen first in 1952 at the age of 45, had suffered three acute attacks of gouty arthritis during the preceding year A family history of gout was denied X ray examination showed a cystic area in the head of the first metatarsal of the left foot He passed a urate stone one year later In the following year, his son, aged 25, had two attacks of gouty arthritis while in the Army The information that his father had suffered from gout was of help in suspecting the correct diagnosis Recently, the daughter, aged 27, passed a calcium stone The concentration of uric acid in the serum of th

daughter was 4 8 mg The relation of the calcium stone to the uric acid disturbance in other members of the family is purely speculative.

The exact mode of transmission of gout has not been determined, because of the insurmountable task of any one observer examining a sufficient number of patients with families big enough to accumulate sufficient data to justify treating the observations statistically Scudamore[213] observed that the father was afflicted

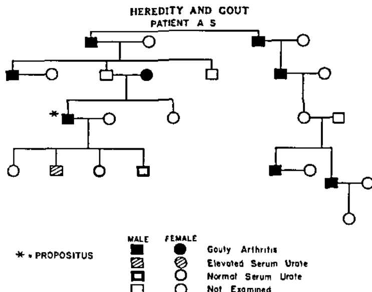


FIG 1 Geneologic data of A S, a patient with a record of gout in the mother and on the father's side

in 87 per cent of the patients with a positive family history Futcher[84] noted the tendency of an affected female to transmit the malady to her offspring In this connection, too, a positive family history has been observed in each of the several females with gout in this clinic

A logical extension of the familial aspects of gouty arthritis has been a geneologic study of the disturbances of uric acid metabolism, a study not possible until the development of clinical

methods for the determination of uric acid in serum Folin, one of the fathers of clinical biochemistry, was among the first observers to report an increased concentration of uric acid in the blood in a nonarthritic relative of a gouty individual.[80] More than two decades later, Jacobson [130] reported similar findings in three nonaffected relatives of gouty persons A comprehensive study of this subject by the author included the relatives of 27 patients with gout.[240] A total of 136 nonaffected relatives were interviewed and investigated with selected procedures as follows (1) inquiry regarding a history of joint distress, (2) physical examination of the joints for the appearance of chronic deforming joint changes and inspection of the ears for the presence of tophi, (3) x-ray examination of the feet in many instances, and (4) determination of the level of uric acid in the serum on one or more occasions Slightly more than one-half of the relatives investigated were males The ages of the subjects ranged from 6 to 86 years, the majority were in the third, fourth or fifth decade of life The history, physical examination and x-ray examination revealed no evidence of gouty arthritis in any of the relatives included in the study, and the presumption of a "non-affected relative" was substantiated.

The negative findings stopped abruptly at this phase of the investigation The concentration of uric acid in the serum was less than 6 0 mg /100 ml in 102 nonaffected relatives The average was 4 6 mg /100 ml This is slightly higher than the average for a similar number of nongouty subjects [240] The remaining 34 non-affected relatives had a serum urate greater than 6 mg The values ranged from 6 1 to 10 8 mg /100 ml The average was 7.3 mg This may be compared with the average value of 8 8 mg for a series of 100 gouty patients In several relatives the elevated values were confirmed subsequently The ages of the 34 relatives with an increased urate concentration ranged from 14 to 86 years Eighty per cent were males The serum nonprotein nitrogen was less than 35 mg /100 ml in each patient In other tests for kidney function in several of the older subjects, each test proved normal It was concluded from the clinical and laboratory data that one of the commoner causes, other than gout, of an elevated concentration of urate in the serum, i e, renal insufficiency, was not responsible

At the same time that this study was under way, Smyth, Cotterman and Freyberg [227, 228] were pursuing a similar project at

Ann Arbor, Michigan Eighty-seven relatives of 19 patients were included in their study. They concluded that genetically "hyperuricemia was presumably due to a single autosomal dominant gene, while only a portion of the heterozygotes for this factor developed clinical gouty arthritis" The lower incidence of gout in females was attributed to the anticipated lower concentration of serum urate in this sex and to a lessened effect of the pathologic gene It is reasonable to believe that the gene for essential hyperuricemia must be considerably more common than one might suspect from the incidence of clinical gout, and the homozygote for this gene should, therefore, be observed occasionally Stecher and associates[235] confirmed these observations but discovered no affected female below the age of 50 in a group of 201 members of 44 families with gout They postulated that normal menstrual function inhibits hyperuricemia Even before the Christian era, it will be recalled, Hippocrates noted the resistance of the female to gout until after the menopause While Smyth and associates concluded from their observations that hyperuricemia was apparently due to a single autosomal dominant, Stecher noted its resemblance to an autosomal recessive in some families but to an autosomal dominant in others

In the most recent study, Haug and Horwald[112] reported the results of an investigation of the concentration of serum urate and blood groups in the case of 261 relatives of 32 patients Fourteen of 45 brothers were found to have an elevated serum urate Nine others suffered from clinical gout The mean value for all brothers was 6 1 mg /100 ml, which may be compared with a mean of 5 1 in male controls The mean for all sisters was 5 4 mg /100 ml, which may be compared with a mean of 4 0 in female controls Blood grouping of the patients and siblings was performed within the systems ABO, Rhesus, MNS, P, Lewis, Duffy and Kell This phase of the study gave no evidence of linkage between the predisposition to hyperuricemia and the genes concerned These observations "do not support the theory of a monomeric, dominant heredity of hyperuricemia, but indicate a cumulative gene action as is the case for normal characters in general"

The several studies of uricemia in nongouty individuals leave unanswered at least three interesting propositions (1) What is the incidence subsequently of attacks of gouty arthritis in nonaffected relatives with an elevated concentration of uric acid in the

serum? (2) At what age is the uric acid elevated in nonaffected relatives? (3) What is the incidence of hyperuricemia in the general population? The few data in each category so far collected in this clinic make only preliminary deductions justified at this time.

A ten-year follow-up of the nonaffected relatives in the series reported in 1940 revealed a low incidence of acute gouty arthritis.[212] The study in the interim decade was conducted partly by mail and

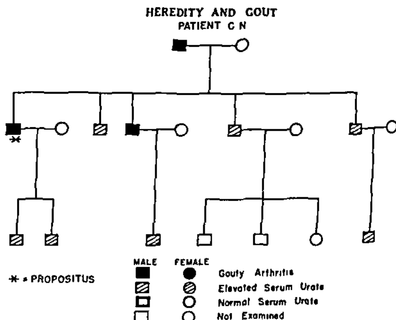


FIG 2. Geneologic data of C N, a patient who died in uremia, having suffered from mild gouty arthritis only

partly by direct contact Information obtained from 80 per cent of the nonaffected relatives showed only 3 of the 34 had experienced one or more attacks of acute gouty arthritis subsequently. Since 1946, a similar study still under way in this clinic on another group of patients, shows the incidence of acute gout in the second group to be not significantly different from the first

In 1948, I was requested to provide terminal medical care for a patient in advanced renal insufficiency with a history of acute attacks of gouty arthritis for almost two decades. Pathologic examination revealed extensive

urate deposits throughout the kidney Investigation of seven male members of his immediate family furnished revealing data (FIG 2) An elevated uric acid was noted in two of his three brothers, both sons, and both nephews X-ray films of the feet in each instance were negative, and there was no history of arthritis in any of the group The increased concentration of urate in the serum of the several members of the family was confirmed from time to time in the succeeding years Uric acid concentrations of 8 6, 7.4 and 7 0 mg, respectively, were observed between 1948 and 1953 in one of the brothers, 50 years of age In the fall of 1954, six years after the initial determination, his family physician reported the sudden onset of acute distress in the great toe and suspected acute articular gout The concentration of uric acid in the serum was 8 7 mg Reference to the original hospital admission of his brother reveals a denial of gout in other members of the family.

Another illustration concerns the father of a patient who had suffered acute attacks of gouty arthritis for more than a decade The propositus was seen first in 1940 at the age of 45 His physician, convinced of the diagnosis of gout, remarked that this represented an instance of spontaneous development in a family without any stigmata of the disease After the immediate problem of management of the acute attack in the son had been resolved, inquiry regarding the other members of the family revealed only two living male relatives of the patient, a 5 year old son and a 78 year old father The father, a vegetarian had chosen a low protein diet as an engineer in the diamond mines in South Africa in the years before World War I, when preservation of meat in the mining settlements was unsatisfactory This 78 year old father was in excellent health and denied, as well as resented implication of, any symptoms in his medical history suggestive of acute gout The concentration of uric acid in the serum however, revealed a value that was similar to his son's, the patient Three years later, at the age of 81, the vegetarian suffered his first attack of gouty arthritis Two years after, he experienced a second attack and died not long after at the age of 83

There are few observations that give any hint as to the age at which an elevated urate concentration in the serum might be observed in susceptible persons [205] One series of observations in our records suggests a progressive increase in the urate level during adolescence

The propositus A S, was seen first in 1949 at the age of 38 with a positive family history of gout (FIG 1) and a personal history of intermittent attacks of acute arthritis for eight years The concentration of uric acid in the serum was 9 9 mg. Blood from his two children was obtained a few months later The concentration of urate in the serum from the daughter, aged 9, was 4 8 mg Lower values were obtained in the subsequent years On the other hand, the son, aged 10 at the initial examination, had a level of 3 4 mg. The

next year it was 3 5 and a year later it was 4 6 mg. and 4 9 mg. The last determination was in 1956 when the son was 15 The values were 5 7 and 6 0 mg

This single series of data does not justify a generalization but suggests that the transition from the normal to the elevated level occurs in adolescence "Though the gout rarely breaks out in regular fits at a tender period of life, the gouty diathesis is often formed at that early age "[85]

The management of the uric acid disturbance in nonaffected relatives has been the subject of some consideration by the writer. Because many of the nonaffected relatives are children or young adults, the significance of the increased concentration has been de-emphasized While mentioning the possibility of gout developing, we have not felt it desirable to recommend a uricosuric agent in any instance E S is an example

While a medical student, E S. volunteered a sample of blood for our control study of uric acid levels The value was found to be 6 8 mg Inquiry into the family history revealed that it was positive for gout Six years later, after he had entered the practice of medicine, and at the age of 29, he suffered the first attack of acute gouty arthritis in the great toe. It is believed that no irreparable harm resulted from ignoring uricosuric agents prior to the initial bout of articular gout. Because of the intimate circumstances, E S has become especially interested in the malady and agrees fully with the conservative regimen prior to the first overt manifestation of arthritis

Since our experience during the past two decades has revealed a low incidence of acute gout developing in the nonaffected relatives, in all probability a higher percentage will not develop gout over a period of time in the future It is likely that a majority of the nonaffected relatives will live a normal span of years without suffering acute attacks at any time Furthermore, the older the individual with an elevated serum urate, the less the chance of acute gouty arthritis appearing Smyth and associates[227] combined their data with ours[210] and estimated that the frequency for all persons carrying the gene for hereditary hyperuricemia would be 0 88 per cent, or a total of 1 2 million persons in the United States This speculation will be discussed also in the section on *Serum Urate Concentration*

Reference was made earlier in this section to the passage of a

calcium stone by the daughter of a gouty patient In another gouty family, there were similar occurrences

In this family there were two brothers, neither of whom had suffered from articular gout One brother had passed a kidney stone at the age of 20, the other had passed brick red gravel on several occasions The serum urate level in the second brother was 6 6 mg /100 ml The propositus, the sister, had suffered from acute gout The concentration of uric acid in her serum was 6 3 mg /100 ml

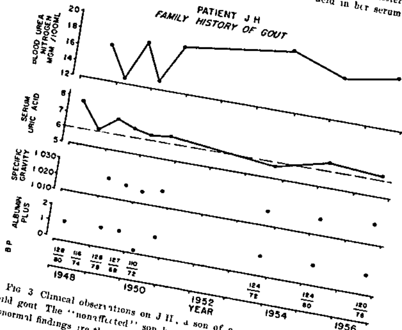


FIG 3 Clinical observations on J H, a son of a patient who suffered from mild gout The "nonaffected" son has had no articular symptoms The only abnormal findings are the persistent albuminuria and hyperuricemia

At the last tabulation there were four instances of renal stones having been passed by persons not afflicted with articular symptoms but members of gouty families, nevertheless

Albuminuria also has been observed in nonaffected members of gouty families

J H, a 30 year old male, is an example (FIG 3) His father, one brother and one sister have gout Albumin in the urine was detected first in J H

symptoms appear in the young, the possibility of gout usually is considered remote The diagnosis may not be taken seriously until after several attacks have occurred and the patient is several years older [10]

One patient in our series developed an acute arthritis in the left hip at the age of 6 A diagnosis of tuberculosis was made and the hip was immobilized for several months Subsequent recovery was satisfactory, but no x ray or bacteriologic evidence supported the clinical presumption of tuberculosis Several joints became acutely inflamed at the age of 12 and persisted for a number of days Acute rheumatic fever was considered likely at this time During the next four years similar attacks of short duration recurred yearly In his late teens, osseous and subcutaneous tophi appeared, and the diagnosis of gout was confirmed. The patient died at the age of 38 with the most extensive chronic tophaceous gout that I have seen.

Schopf [211] reports a fabulous example of tophaceous gout in a 5 week old infant The family history was negative for gout The periarticular tophi grew with extraordinary rapidity. Postmortem examination, following death from pneumonia, revealed urate deposits in the joints, soft tissues and kidneys No note is made regarding the possibility of a fulminating blood dyscrasia being responsible for the increased formation of uric acid, as in the 5 year old boy reported by Vining and Thomson [257] One of the youngest examples of primary gout was studied by Rausch.[196] The patient was a 23 year old girl with chronic tophaceous gout who suffered the first articular attack at the age of 3

At the end of life's span, on the other hand, is the male discussed in the section on *Heredity*, who had his first attack at the age of 81 His son had suffered for many years from gouty arthritis The concentration of uric acid in the serum on the father, three years before his first attack appeared, was 8 2 mg He died at the age of 83, having experienced only two attacks of acute gout. These examples illustrate extremes The vast majority of patients are afflicted with the initial attack in the middle years of life The disease tends to be more severe and to show more extensive joint involvement in those whose symptoms begin early in life [94] Patients developing clinical gout after the fifth and sixth decades of life rarely develop crippling deformities of the joints and are no more prone to renal or vascular complications than are nongouty patients of the same age The case of M Quartier, Physician to the Duc de

Bouillon, who died at over 100 years of age, is noteworthy Although he had suffered from gout upward of 60 years, yet "ten years before his death he was seen to walk as firmly as if he had never been afflicted with the disease "[83]

Race

The malady is believed to be widely distributed throughout the world although documentary evidence in support of this statement is lacking The incidence in England and Central Europe has received particular attention because of the numerous monographs and case reports in the medical literature of the respective countries The English and German physicians were interested in gout and wrote extensively on the subject If a similar interest had been manifest in other countries, undoubtedly the disease would have been found to have been more widely distributed than is apparent from the medical literature Casual conversation with rheumatologists from several countries in South America reveals a consensus that the incidence is low On the other hand, where a specific interest in the disease is apparent, as in one clinic in Montevideo, Uruguay, more than 60 cases of gout were discovered in a period of a few years,[174] and Moreno[176] reported a series of 123 cases in Buenos Aires Argentina An exceptionally high incidence among natives of India has been noted[61 73] Instances of chronic tophaceous gout have been observed in native Chinese[187 213] Berk[19] describes one case of chronic tophaceous gout in a Filipino, and uncovered another case in the hospital records Mackler[159] observed three cases in Filipinos, one with bilateral olecranon tophi The Negro race is presumed to be relatively immune to the malady A number of case reports have appeared during the past 20 years,[83 189 254] however, and the earlier impressions regarding incidence must be modified Cohen[55] has reported three instances of gout in Negro brothers, and has studied the geneologic tree for four generations Recently we have examined the postmortem specimens of a Negro female with many tophi

Social Status

The disease is not a result of a gluttonous appetite, indulgence in alcohol or any other culpable weakness of a particular group of persons This fact is contrary to the impression of Sydenham that

gout attacks the rich more frequently than the poor.[238] Gout is a familial malady and the susceptible may develop clinical evidence of the ailment, irrespective of these several factors. It is recognized at the present time that the indigent and the well-to-do may suffer from this affliction. Admittedly the standard of living in America has been rising steadily for several generations, concomitant with a greater number of cases being reported decade by decade. The increase in incidence, however, is apparent, not real. Gouty arthritis should be suspected in any individual, independent of the social status if the clinical characteristics are present.

Season

For centuries, the incidence of acute articular episodes has been associated with particular seasons. Gairdner[85] noted that ". . . for several years he (a patient with gout) had never missed a severe fit in the autumn and rarely in the spring." Williamson[267] found that the April-May and November-December periods displayed the highest incidence. Brochner-Mortensen[38] confirmed the April-May peak but not the fall peak. March seems to be a particularly vulnerable month for our patients, and the months in the fall somewhat less. The only suggested clues are the wide and deep swings in barometric pressure with stormy weather. A correlation between decrease in barometric pressure and onset of articular distress was reported from our laboratory a number of years ago.[247]

Etiology

ALTHOUGH THE ETIOLOGY of gout is not defined clearly, an increasing volume of evidence supports one explanation among the several advanced as likely possibilities. Pertinent to a discussion of etiology are at least three accepted facts inherent in the disease. First, observations show the malady to be familial in distribution and reveal the deviation from normal function to be transmitted directly; secondly, an increased concentration of uric acid in the serum is one of the objective manifestations of the dyscrasia that is readily determinable. Thirdly, a number of patients with gout excrete unusually large amounts of uric acid in the urine on a con-

trolled low-purine intake In substance, the increased concentration of uric acid in the serum and body fluids is believed to result from an overproduction of this normally occurring product of metabolism This phenomenon is the inborn error The deposition of uric acid in the joints and the acute attacks of articular distress, subsequently, are incidental to the basic metabolic fault.

An increased concentration of urate in body fluids may be a resultant of external factors or may be brought about by internal derangements Improper diet, excessive intake of alcoholic beverages and exposure to lead, among other items, have been implicated as external noxious forces Except for an abnormally high intake of purine substances, there is little evidence to implicate any one of these factors, or a combination, in the etiology of the metabolic dyscrasia. It is reasonable to postulate, on the other hand, that endogenous factors concerned with the intermediary metabolism of purine substances and other precursors of uric acid are responsible for the underlying defect

There are at least three likely internal dysfunctions which might lead to an increased concentration of urate in body fluids These are

1 Diminished destruction by enzymes

2 Diminished excretion by the kidneys

3 Increased formation through a fault in intermediary metabolism The third possibility is believed to explain best the experimental observations.

Destruction by the human organism of significant quantities of uric acid by an enzyme system comprising uricase is not of sufficient magnitude to explain the metabolic phenomenon When comparison is made with selected lower animals, the concentration of this uricolytic ferment in human tissues, except in the liver and intestine, is not high Uric acid oxidation has been detected by cytochrome oxidase,[59] lactoperoxidase, vertoperoxidase and catalase [51] Also, Bien and Zucker have measured uricolysis when uric acid has been incubated with human erythrocytes or leukocytes [24] Since the degradation product of uric acid in lower animals is allantoin, presumably the action of uricase in man would produce the same end-product Again, since nongouty humans excrete only a few

milligrams of allantoin daily, a deficiency of the uricase enzyme system in gouty persons seems unlikely.

The failure to detect significant quantities of uricase in man does not preclude uricolysis with finality. When uric acid labeled with N^{15} has been injected into a human subject, a portion of the isotope has been excreted as urea. On the basis of isotope recoveries, Wyngaarden and Stetten[277] calculated that 18 per cent of the uric acid administered was degraded to other nitrogenous products which were recovered in the urine. A smaller percentage was excreted in the feces. In order to exclude uricolysis by intestinal bacteria, the experiment was repeated while intestinal bacteriostasis was maintained by an oral sulfonamide. The results were essentially the same. Recovery studies in our laboratory[48] revealed a somewhat smaller N^{15} urea and ammonia incorporation than observed by Wyngaarden and Stetten. The recovery in the urine of intravenously injected N^{15} uric acid in six gouty subjects was less than in the normal controls In three of these experiments the recovery of N^{15} as fecal nitrogen was somewhat above normal. It is apparent that there is some destruction of uric acid in the normal as well as in the gouty subject, but no mechanism of impaired destruction accounts in essence for the increased concentration of urate in body fluids

Diminished excretion of urate by the kidneys has enjoyed limited popularity as an explanation of the increased concentration in the serum Garrod[89] is accredited with this hypothesis, which found a strong supporter in Thannhauser.[250] There is some question, however, whether Garrod was committed to this hypothesis, for in his original dissertation[88] he expressed grave doubts as to its validity. If this theory is valid, selective impairment in the kidney, specific for excretion of uric acid, should be responsible for the disturbance without impairment necessarily of the other functions of the kidney The evidence in this sphere of physiology bears examination It is generally agreed, on the basis of results from routine clinical tests, that gouty subjects in the earlier years of the disease, and particularly in its milder form, show normal renal function Likewise, the studies on glomerular filtration rate, blood flow and maximum excretory or resorptive capacity have led to similar con-

clusions.[20, 58] As acute articular attacks recur and the disease progresses, one or more indices of renal insufficiency frequently show evidence of deterioration A small quantity of albumin in the urine, cylindruria and inability to concentrate solids maximally, or a persistent decrease in the rate of formation of glomerular filtrate do not produce recognized clinical symptoms Laboratory procedures, however, if utilized in the search for such irregularities, may reveal one or more of the stigmata of kidney dysfunction Later in the course of renal impairment in a few afflicted persons, the specific gravity is fixed, the excretion of phenosulfonphthalein is depressed, glomerular filtration rate is reduced to a critical level and the concentration of nonprotein nitrogen in the serum is elevated These findings, representing late manifestations of kidney dysfunction in gouty persons, are observed in a limited number of patients only The point to be stressed is that kidney function in patients with gout should not be called normal if any one of the above-mentioned findings in minimum, moderate or severe degree, is observed Moreover, the kidney in gouty persons should be investigated with as many independent procedures as possible since the early evidence of insult to the kidney may be singular and not multiple

Studies designed to evaluate renal exchange of urates reveal little difference between gouty patients and nongouty controls Likewise, uricosuric drugs, such as Diodrast or Benemid, alter urate resorption in a similar fashion in gouty and nongouty subjects, if kidney damage is absent The faculty of the kidney to maintain urate clearance in gouty patients with a decreasing glomerular activity bespeaks superior rather than inferior ability of the excretory apparatus to handle urates This adjustment continues into the preterminal stages of renal insufficiency Gouty patients with azotemia may have an essentially normal urate clearance but a depressed urate reabsorption of 30 or 40 per cent[56] Urate clearance approaches zero in the terminal stages of renal impairment because of a critical depression in glomerular filtration rate

It was believed, and so stated a number of years ago, that a constitutional inferiority of the kidneys of gouty patients to excrete uric acid had not been demonstrated, and that renal changes in patients with gout were the result of gouty and ancillary nongouty

processes and were not the cause of the metabolic dyscrasia.[247] At that time, the concept of active secretion of uric acid by the tubule had long since been abandoned. This subject has been reopened by Thannhauser,[251] who concedes that his original explanation of constitutional inferiority of the kidney in martyrs to the disease was based upon the theory of active tubular secretion of uric acid. Nevertheless, he is reluctant to abandon the impaired excretion theory and concludes that "One seems justified in assuming that tubular reabsorption of uric acid may vary in the healthy person but remains at such a high level in the gouty person that hyperuricemia becomes permanent and precipitation of uric acid in the tissues results." This conclusion is highly speculative and is inconsistent with contemporary experimental observations on the dynamics of the kidney.

Increased formation of uric acid by the body leading to an increase in the size of the metabolic pool is believed to be the most satisfactory explanation for the metabolic disturbance. An increased metabolism of purine substances and a concomitant increase in urate content of body fluids need be but slight to account quantitatively for the chemical irregularities in gout. Also, the overproduction hypothesis would be consistent with the excretion of abnormally large amounts of uric acid in the urine as observed in some patients. The writer is partial to this theory because most of the observations collected in his laboratory have supported it indirectly, although conclusive evidence had not been forthcoming until a few years ago. Recently, increased uric acid synthesis in gout has been demonstrated by isotope studies utilizing N^{15}-labeled glycine. Ingestion of this substance results in a higher concentration of N^{15}-uric acid in the urine of victims of gout than in controls. Benedict and associates [19] have assumed that the increased formation of urates occurs at the expense of urea and enjoys a more direct pathway. This assumption has been confirmed by Muller and Bauer [179] and by Bishop and associates.[29]

A tabulation of the glycine incorporation studies by the investigators interested in this problem reveals that somewhat less than one-half of the patients with clinical gout show this abnormal function of intermediary metabolism. Benedict and associates, in a subsequent study, noted an abnormally rapid incorporation of

dietary glycine nitrogen into uric acid in the case of subjects exhibiting abnormally high basal uric acid excretions. Patients with a basal excretion essentially normal showed no accelerated uric acid synthesis. It appears that in some, but not in all gouty patients, a shunt will be demonstrated whereby dietary glycine nitrogen enters the purine nucleus of uric acid more promptly than in the normal, presumably without the obligatory intervention of the nucleic acid purines. Although there have been no reliable clinical features in differentiation, Gutman and Yu [107] have speculated on the possibility of two types of uric acid disturbance in gouty patients. Admittedly, it is difficult to reconcile the discordant data, and logical to accept the existence of two types of gout, but I am of the opinion that an increased formation of uric acid is not detected in all patients with gout because of a deficiency in our laboratory procedures.

These collected observations are interpreted as favoring the explanation of an increased formation of urate by the body as the etiologic mechanism and provide meager corroboration of the other possibilities. The metabolic defect, then, is a partial reversion to the normal situation in birds and reptiles, namely, a significant *uricotelic* component in a predominantly *ureotelic* species. Ancillary data also support this explanation. The increased concentration of serum urate in nonaffected relatives in all likelihood is caused by the trait. Patients with polycythemia vera and other blood dyscrasias, maladies known to be associated with an increased metabolism of purine substances, may develop gouty arthritis as a complicating malady. The articular and renal findings are similar to hereditary gouty arthritis.

Before dismissing etiology, we should mention two other aspects of this subject that have received considerable attention in the literature, i.e., an endocrine and an allergic cause of gout, respectively.

There have been attempts from time to time to identify gout as an "endocrine" disorder. To be sure, Hippocrates observed that females do not suffer from gouty arthritis until after the cessation of the menses, but only recently has an endocrine etiology been championed. Wolfson and associates [272] reported a decreased excretion of 17-ketosteroids in the urine of gouty patients with normal

biologic androgen activity The formation of an abnormal androgen in gouty patients was postulated This dysfunction has not been confirmed nor has a consistent decrease in 17-ketosteroid excretion in gouty subjects been observed by other investigators[47, 130, 148] The only reproducible association of gout and an endocrine dysfunction is related to the inception of the acute gouty episode The manifestation of stress agents may be detected by a sudden increase in secretion of adrenocorticotropic hormone with a decrease subsequently, to a subnormal level. An acute attack of gout sometimes follows such an event. More than two decades ago significant changes in electrolyte metabolism associated with an acute attack were demonstrated that could be attributed to hyperactivity of the adrenal cortex[248] Also, Hellman[113] noted that acute articular gout might be precipitated by the administration of adrenocorticotropic hormone Until further evidence is forthcoming, it must be concluded that gout is no more a disease of the endocrine glands than is rheumatoid arthritis

Nor is there any better evidence that gout is an allergic dyscrasia Harkavy[109] reported that anti-allergic measures were effective in controlling acute symptoms. I find it difficult to subscribe to this theory generally, nor have stubborn attacks of gout responded to antihistaminic drugs in selected instances in this clinic.

—Intermediary Metabolism of Uric Acid—

NOSOGRAPHERS HAVE INCLUDED gout in comprehensive presentations of metabolic disorders since this category has been defined in clinical medicine It was noted in the monograph published in 1943[240] that. "The classification of gout as a metabolic disorder is believed by us to be expedient, but our reasons for this are based upon diverse data and not because a disturbance of the intermediary metabolism of nucleoprotein and purine substances has been demonstrated " In the intervening years, a disturbance of intermediary metabolism has been demonstrated and the assumption has been supported by experimental evidence. The significant advances in the understanding of the uric acid disturbance may be documented

Precursors of Uric Acid

The chemical formula of uric acid was shown by Fishe be 2-6-8 trioxypurine with the "lactam" formula Uric acid end-product of metabolism of purine substances in humans, urea is the end-product of the nitrogenous substances of amino and pyrimidin origin Most other mammals convert uric aci

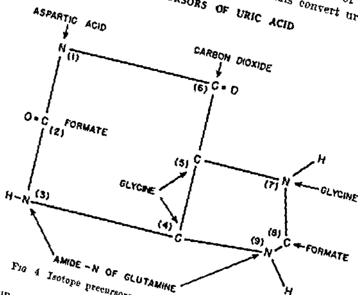


Fig 4 Isotope precursors of uric acid in the human body

allantoin and excrete only small amounts of the former substance Virgin reptiles excrete uric acid as the end-product of nitrogenous substances whether of purine or amino acid origin Uric acid is excreted in relatively constant amounts in humans and is little affected by variations in dietary intake except for purine or nucleic acid substances[208] Uric acid excreted by man is partially endogenous and partially exogenous At least 300 mg of endogenous urates are lost in the urine daily[209] on a purine-free diet with an adequate calorie intake An additional 200 mg may be disposed of by way of the intestinal tract and the sweat glands

Recent studies, utilizing isotope technics, have contributed greatly to the understanding of the sources of endogenous uric acid, in lower animals as well as in humans It is generally accepted that mammals are capable of synthesizing purine bodies and converting them to uric acid [52] The constituents that may be incorporated in the purine ring (FIG 4) include glycine, which furnishes carbon atoms 4 and 5, and nitrogen atom 7, while carbon dioxide

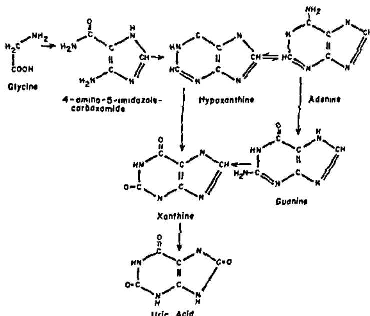


FIG 5 Pathways of purine metabolism in the human body.

supplies carbon atom 6 Formate supplies carbon atoms 2 and 8 Nitrogen atoms 3 and 9 come from the amide-N of glutamine, and nitrogen atom 1 comes from aspartic acid The first reaction of glycine is a combination with phosphoribosylamine to yield glycineamide ribotide Several intermediates are then formed in the steps to inosinic acid One of these compounds has been identified as 4-amino-5 imidozole carboxamide, which is converted to hypoxanthine (FIG 5) The synthesis does not produce free hypoxanthine, but hypoxanthine nucleotide, or the compound known as inosinic

acid Hypoxanthine is synthesized initially, adenine and guanine are formed from it by amination Guanine, at least, must be in combination with desoxyribosphosphoric acid in synthesis since it has been shown that administered guanine is not incorporated into body nucleic acid In birds and reptiles, the synthesis of hypoxanthine, as outlined, is used not only for the formation of nucleic acid but also for the conversion of waste ammonia to uric acid Even in mammals, recent experiments indicate that although the bulk of ammonia is converted to urea, some ammonia is converted rapidly into uric acid, apparently through the hypoxanthine mechanism Hypoxanthine is oxidized by xanthine-oxidase to xanthine and subsequently, to uric acid

The pathway of degradation of glycine to uric acid for non-gouty subjects is through adenine and other purine substances to nucleic acid and eventually to uric acid A more direct pathway from glycine to uric acid is responsible in the gouty subject [23] The feeding of labeled glycine results in a higher maximum and a more rapid decline in the N^{15} concentration in urinary uric acid Furthermore, the fraction of isotope administered which is excreted as uric acid is greater in the normal than in the gouty patient The maximum values for N^{15}-urinary uric acid are produced on the second day in gouty patients, and on the third or fourth days in the controls The effect of total protein intake upon the conversion of dietary glycine into uric acid has been investigated also N^{15}-labeled glycine, has been administered to a patient with and without fortification of the diet with milk protein [24] An increase in protein consumption in each subject favored the conversion of dietary glycine to uric acid and paralleled an increase in the conversion of glycine nitrogen to other products However, the percentage of excreted N^{15} which appeared in uric acid was not sensibly altered by the change of diet Seegmiller and associates [25] have investigated the incorporation of 4-amino-5-imidazole carboxamide-4-C^{13} into uric acid in the normal human The experimental substance was ingested and recovery of C^{13} in the urine determined The peak concentration of C^{13} in uric acid was reached in 14 hours Approximately 25 per cent was recovered in uric acid during the following three weeks Thus, a mechanism for prompt conversion of this precursor to uric acid as well as a second, less direct, mechanism by way of body purines has been demonstrated

Miscible Pool and Turnover Rate of Labeled Uric Acid

These functions, miscible pool and turnover rate, comprised the first phase of the isotope studies which proved to be critical in the investigation of the disturbance of intermediary metabolism "The miscible pool of uric acid has been defined as that quantity of uric acid in the body of the subject which is capable of mixing promptly with intravenously injected uric acid and, consequently, of diluting its isotope From a comparison of the concentration of N^{15} in the uric acid injected and in that present in the body at the moment of mixing, together with knowledge of the quantity of uric acid injected, *the quantity of uric acid present in the miscible pool* may readily be calculated "[236] It is possible to prepare labeled uric acid with an over-all concentration of N^{15} as high as 32 per cent atom excess Not more than 25 mg. of purified labeled uric acid is necessary for a single test, an amount which may be injected intravenously as a neutral solution without untoward effects. Complete urine samples are collected for approximately one week and partitioned into four or six-hour periods. The uric acid is isolated from the urine samples, converted to ammonia by the Kjeldahl procedure and subsequently broken down into nitrogen Determinations of the ratio of N^{15} (heavy nitrogen) to N^{14} (naturally occurring nitrogen) is made in a mass spectrometer. It should be noted that heavy nitrogen is not radioactive, nor is there any recognized harm from the parenteral administration of the labeled compounds

Bishop and associates[47] have made several assumptions in the determination of the metabolic pool size and turnover rate following injection of isotopic uric acid into normal or pathologic subjects These are as follows

1. "All the uric acid in the body that participates in the metabolic pool is freely diffusable and at the same concentration. This total amount of uric acid is identified as the body pool, miscible pool, or metabolic pool of uric acid

2 "The size of this pool (in milligrams or in millimoles of uric acid) is homeostatically fixed (constant). This implies that the rates of origin and disposal are equal.

3 "Intravenously injected, isotopical [illegible] l uric acid mixes completely and immediately with all the uric [illegible]

4 "The mo[illegible] of isotopic uric [illegible] [illegible]inguishable from the naturally [illegible] les insofar [illegible] [illegible]cesses or excretion [illegible]

5 "The uric acid synthesized by the body contains no N^{15} in excess of normal abundance. No catabolic fragment of enriched uric acid is reused for uric acid synthesis Furthermore, no uric acid escapes from the body pool at a later time after the isotope concentration of the pool is changed

6 "The concentration of isotope in the uric acid collected in the urine during a particular period is the same as the concentration of isotopes in the uric acid of the body pool during that period

7 "Uric acid is excreted in the urine at a relatively constant rate."

If these assumptions are correct, the mathematical expression of the fall of the isotope concentration of urine uric acid as a function of time may be described as a differential equation When the logarithm of the isotope concentration of the urine uric acid is plotted against time, a straight line results

The metabolic pool, or miscible pool, of uric acid for humans has been determined in several laboratories, and the agreement for nongouty controls without a demonstrable disturbance of uric acid metabolism has been found to be remarkably constant The pool size for a normal individual, as determined in Stetten's laboratory,[15] ranged from 1145 to 1341 mg Geren and co-workers[31] determined the pool size in one normal to be 944 mg A range of from 731 to 1238 mg was observed in the author's studies[27] The data for the turnover rate of the miscible pool likewise show satisfactory agreement among the several laboratories The turnover rate for normals, as observed by Stetten's group, was 0 53 to 0 76 pools per day Geren observed the turnover rate of 0 83 pools per day, while Bishop, Garner and Talbott observed a range from 0 59 to 0 96 pools per day

The miscible urate pool of patients with gout, on the other hand, was greater by twofold or more, and the turnover rate considerably less than for the nongouty person These findings were independent of the presence of symptoms of acute or chronic gouty arthritis Several selected observations are given in TABLE 1 The uric acid in the isolated deposits in the gouty subject is largely ignored in these mathematical considerations. Undoubtedly, there is some interchange between the uric acid on the periphery of the tophi and the uric acid in solution in body fluids immediately adjacent The interchange, however, is believed to be so slight as to exert no detectable effect upon the values of the metabolic pool and turnover rate This conclusion is based upon the observation that it may require several

years for visible tophi to appear in patients with gout Stetten is of the opinion, however, that the interchange is appreciable in some patients [237] The magnitude of the miscible pool in one subject with *tophaceous* gout was far greater than could be assumed to be present in solution in body water because of the relative low solubility of uric acid in body fluids. In fact, the isotope calculation revealed that more uric acid was in the solid phase, tophi, than in solution [14] Data of this magnitude have not been observed in our laboratory

The determination of the miscible pool and turnover rate following the injection of labeled uric acid enhances our understanding

TABLE 1 *Experimental Observations upon Metabolic Pool and Turnover Rate in Normal and Pathologic States*

SUBJECT	CLINICAL DIAGNOSIS	METABOLIC POOL SIZE	TURNOVER RATE
		Mg	*Pool/Day*
G W	Normal	1019	0 78
C C	Rheumatoid Arthritis	1228	0 83
S K	Rheumatoid Arthritis	951	0 90
T J	Normal	874	0 64
K J	Polycythemia Vera	1054	0 68
B S	Gout	3031	0 50
S W	Gout	3430	0 49
D G	Gout	2014	0 39
B M.	Gout	1952	0.42

of the metabolic dyscrasia in at least two categories The observations support the presumption that there is an increased formation of uric acid in the gouty subject Furthermore, the procedure may be an intriguing experimental tool for the study of the effect of anti-gout drugs Potent uricosuric substances lead to a decreased concentration of urate in the serum, a decrease in the size of the metabolic pool and an increase in the turnover rate The first uricosuric substance to be studied in this regard was sodium salicylate Benedict and associates [14] reported a marked diminution in the metabolic pool following prolonged administration of salicylates ACTH and cortisone are mildly uricosuric agents and result in a modest effect upon the size of the metabolic pool in gouty patients [244]

A decrease in the metabolic pool following the ingestion of Benemid has been observed by Bishop and associates [29] The metabolic

pool decreased from 2205 mg to 1622 mg in one experiment, and the turnover rate increased from 0.48 to 1.00 pools per day. Collection of the second series of observations began on the third day of the Benemid regimen. The data illustrate the rapid response by the body to this uricosuric agent. To date, the evidence suggests a persistent effect upon the metabolic pool during the ingestion of Benemid.

The Influence of Diet and Total Caloric Intake

One of the first controlled studies of the influence of proteins upon excretion of uric acid was reported by Folin in 1905.[77] The addition of protein to a purine-free diet resulted in an increased excretion of uric acid. Host,[122] in 1919, observed significant variations in uric acid excretion on a diet essentially free of purine substances. An increase in the protein intake and a reduction in the carbohydrate intake increased the uric acid output. When the protein intake was maintained constant, a reduction in the caloric intake decreased uric acid excretion. This result is not surprising in view of studies in recent years utilizing isotopes and identifying precursors. Bramik[37] has measured the endogenous and exogenous urate excretion in a normal control and in one gouty individual. The level of endogenous uric acid excretion on a purine-free diet was reached in five days in the normal and in fourteen days in the gouty subject. During a seven-week study period it was calculated that the gouty subject retained 271 mg of uric acid daily, an amount in excess of 76 Gm in a year. This value appears to be reasonable.

In a study of the action of amino acids upon uric acid excretion by Lewis and associates,[149] they found glycine and alanine caused a sharp increase in the excretion of uric acid while ammonium chloride or urea produced no effect. It was suggested that the increased excretion produced by amino acids resulted from increased cellular metabolism. Using a different approach, Wilson and associates[264] observed that significantly more uric acid was excreted on a high protein intake than on a high fat diet. A high carbohydrate diet yielded results intermediate between the other two. In a study by Folin and associates[79] of the action upon the concentration of uric acid in the serum of a high protein intake combined with a diet free of purine substances, they found a decrease in the concentration of uric acid in the blood with a corresponding increase of uric acid

in the urine Bishop and Talbott[30] have attempted to reconcile these and other conflicting observations and hypotheses in regard to the influence of dietary substances upon uric acid metabolism in man

"In humans, on a purine-free diet, uric acid is derived from the break down of purines and nucleoproteins (endogenous, wear and tear source) and by more or less direct synthesis from the metabolic pool as is common in birds and other animals When the nitrogen pool is well stocked after protein or amino acid feeding, more uric acid is synthesized by the second route and the overall uric acid output is increased After the feeding of fats, there is a greater preponderance of acidic fragments to be disposed of, and these require more ammonia for neutralization at the kidney level Thus, nitrogen is lost from the metabolic pool, and the direct synthesis of uric acid is curtailed There is no need for marked acidosis or ketosis at this point since the changes might well be so slight as to go unnoticed A high calorie diet has a nitrogen sparing action which allows more uric acid formation per gram of nitrogen ingested. On a low calorie diet the amino acids are expended more prudently because they must supply both protein synthesis and energy requirements and are not so readily available to the general metabolic pool"

The subject of diet will be discussed again in the section on *Therapy* It should be noted that some of the experimental observations and deductions are not substantiated by clinical experience Theoretical consideration suggests that greater emphasis be placed upon the dietary control than has been found to be necessary empirically

Urate Concentration in Serum

THE PHYSICO-CHEMICAL STATE of uric acid in body fluids has commanded the attention of biochemists for decades. Particular scrutiny has been given the possibility that uric acid exists in forms other than as simple molecules in true solution. The presence of uric acid in a dimeric, polymeric or colloidal form or as a protein-bound moiety has been entertained Gudzent[102] concluded in 1918 that uric acid exists in the blood only in the form of the monosodium salt. On the other hand, Bornstein and Griesbach[33] stated that approximately 50 per cent of the blood uric acid was in a combined form unable to migrate through a cellophane membrane. Theoreti-

cally, small molecular aggregates of uric acid would be ultrafiltered, while polymeric and colloidal forms would not Some investigators have assumed that there are significant differences in gouty and nongouty subjects in the percentage of *bound* to *total* uric acid Recently, Jorgensen and Neilsen [132] concluded that uric acid in the plasma is present as the free ion only The possibility that some uric acid in the red blood corpuscles is present as a riboside or a ribotide originally, and is split off in the preparation of the material for quantitative analysis has been entertained The clinical implications of these several investigations and speculations are not disturbing Each biochemical laboratory should set up its own range of serum uric acid values for gouty and nongouty subjects and interpret the values upon the basis of such experience

Urates are present in body fluids in concentrations considerably less than the maximum solubility of sodium urate in distilled water Concentrations in distilled water as high as 100 mg./100 ml have been reported The lower values for maximum solubility in body fluids are due to the presence of other substances. Gudzent [100] obtained a final solubility in serum equivalent to 8 3 mg./100 ml., while Bechold and Zeigler [13] obtained solubilities over 20 mg./100 ml When uric acid is added in vitro to serum of gouty patients, concentrations as high as 25 mg./100 ml may be obtained within a few hours [249]

The low solubility of urate in body fluids, which contributes to the predisposition to precipitation in bones and soft tissues in the gouty person, has not always proved a handicap to organisms [120] The insolubility of uric acid has been of considerable teleologic value to birds and reptiles by permitting the successful development of the embryo in a hard shell The purine substances from nucleic acids and the ammonia from amino acids were converted to uric acid and excreted through the kidneys of the embryo as a dilute solution The water was retained ultimately, leaving the uric acid as a solid mass in the allantois If highly soluble urea had been evolved instead of uric acid, the water could not have been absorbed against the gradient of the increasingly concentrated urea solution The embryo would then have died from dessication or from uremia *Adult birds and reptiles and, to a lesser extent, man,* have retained the uricotelic mechanism.

The determination of serum urate content is carried out in the routine biochemical laboratory usually with one of the standard methods.[18, 73] Whole blood is a less desirable medium than serum or plasma for the determination of uric acid, because of the unequal distribution of urates between cells and plasma as well as because of the presence of interfering substances in red cells. The interfering substances are particularly troublesome in the colorimetric procedure. In an investigation of the ratio of uric acid between plasma and red cells a number of years ago in our laboratory,[219] the ratio in the aqueous phase of cells and plasma was approximately 0.60 as determined by the colorimetric method of Benedict. Jorgensen and Nielsen,[132] using an enzymaticoptic method, confirmed in essence these earlier studies and reported that the ratio averaged 0.55.

Reagents for the determination of uric acid should be freshly prepared at frequent intervals, and one technician in each laboratory should be responsible for the procedure. It is particularly important to secure reliable information regarding the abstinence from or administration of uricosuric agents prior to the collection of blood for the determination. Since salicylates are analgesic as well as uricosuric and are frequently contained in proprietary remedies in the treatment of arthritis, prior ingestion may depress the concentration of uric acid to produce equivocal results. Without specific questions as to the prior ingestion of drugs, the facts may not be revealed. At least 48 hours should elapse between administration of an analgesic uricosuric agent and the collection of blood for uric acid determination for diagnostic purposes.

The concentration of uric acid in *serum* in normals is less than 6 mg./100 ml. In patients with gout, irrespective of the presence of acute or chronic symptoms, and irrespective of the stage of the disease, the concentration is greater than 6.0 mg. This lower limit for most gouty patients is maintained except for the administration of uricosuric agents. For practical purposes, these are the anti-gout agents such as salicylates, Benemid, phenylbutazone and the steroids. The range in serum for gouty patients, except during the administration of a uricosuric agent, is between 6 and 10 mg. (FIG. 6).

In a study of 157 individuals between the ages of 5 and 60 years, Greisheimer and Arny[65] noted the *whole blood* levels to be 3.07 mg. for females, and 3.42 mg. for males. This is but one of several

observations that suggest a slightly lower range for females than for males Smyth and associates[231] have recommended revision of the standards so that the accepted range for females would be approximately 0 5 mg lower than for males If this suggestion is followed, the upper range in serum for normals should be 4 5 mg for females, and 5 0 mg for males, and the lower limit for gouty subjects should be 5 5 mg for females, and 6 0 mg for males The

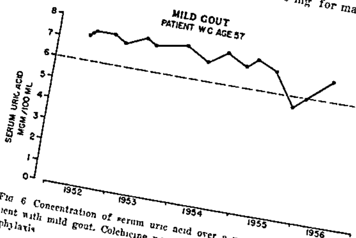


FIG 6 Concentration of serum uric acid over a period of four years in a patient with mild gout. Colchicine was the only drug prescribed regularly in prophylaxis

case of a 34 year old housewife illustrates the lower value in a female

M K has suffered intermittent attacks of acute gout over a period of nearly three years with the metatarsal phalangeal joint of the great toe usually the afflicted site Response to colchicine has been excellent X ray films of the feet show punched out areas, suggestive of osseous tophi Thus, the clinical diagnosis is based upon satisfactory criteria Uricosuric agents were not recommended originally, and several samples of blood were taken for the urate level Specifically, seven determinations of uric acid showed concentrations ranging from 4 5 to 6 0 mg /100 ml

Admittedly, the higher values are borderline, but if this were a male with several attacks of gout, on the basis of our clinical experience, the values would be somewhat higher

The uric acid level in normal infants is considerably less than in adults. Liefman[119] reported values of 1 3 to 1.7 mg. in infants on a diet containing purine substances It increased slowly up to 2 4 mg in growing children Another interesting study was reported by Starkenstein,[234] who followed the excretion of uric acid in the urine of a child over a period of sixteen years. The excretion increased gradually from an average of 120 mg. per day to 440 mg at the age of 18 Hoeffel and Moriarty[119] noted that the average level of uric acid in the blood during the first two years of life was 3 1 mg., between the ages of 2 and 15 years it was 3 8, and in adults it was 4 1 mg

The concentration of urate in retained body fluids, with the exception of spinal fluid, is similar to that of a protein-free filtrate of plasma In a number of opportunities to collect synovial fluid and serum simultaneously, we have found an excellent agreement on the basis of a protein-free filtrate The low concentration of uric acid in spinal fluid has been attributed to the blood-brain barrier, a phenomenon not adequately understood

The concentration of serum urate may be elevated above the normal range in several states not usually associated with clinical gout Kidney insufficiency, either acute or chronic, is the most common cause encountered In the early part of this century the clinical biochemist was hopeful that the level of uric acid in the blood would prove to be endowed with prognostic significance in patients with renal impairment It is believed now that the increase in concentration of uric acid in body fluids in renal disease is merely a reflection of the inability of the kidney to excrete nitrogenous end-products Patients with myelofibrosis, leukemia, or polycythemia vera may show an increased concentration of uric acid in the serum Isolated examples that have been reported in other conditions include pernicious anemia, lead poisoning, starvation, asthma, carcinoma, eczema, cardiac failure, lobar pneumonia, coronary insufficiency, myocardial infarction and eclampsia. With the exception of the blood dyscrasias, the elevation of uric acid in the serum is not associated with articular symptoms. The increased metabolism of nucleoproteins is believed to be the explanation of the increased urate content The increased concentration in nonaffected relatives has been discussed in the section on *Heredity*. There remains yet

another group of patients with an elevated serum urate. These are suffering from what appears to be typical rheumatoid arthritis. The incidence of an elevated serum urate in rheumatoid arthritis is noteworthy, even though the finding may confuse the attending physician. It is our belief that the clinical diagnosis of rheumatoid arthritis outweighs heavily any laboratory finding if this is the only datum in support of a diagnosis of gout. It would be of considerable academic interest to determine the level of uric acid in the serum of a large number of patients with rheumatoid arthritis. Diagnostic implications, however, need not be altered.

The incidence of idiopathic hyperuricemia is not known but is believed to be appreciable as judged from our observations. Submission of blood for urate concentration has been encouraged for a number of years from patients with or without a clinical suspicion of gout. I am amazed at the number of elevated values that are discovered in patients without good clinical evidence to explain this phenomenon. Several years ago more than 1500 samples of blood were obtained from college students 18 to 21 years of age, during their routine medical examination. Sixty-eight of the students had a serum urate level greater than 6 mg./100 ml. The elevated levels were confirmed in most subjects at a subsequent examination. No satisfactory explanation of the elevated values was deduced in most instances. A personal history of gouty arthritis, a blood dyscrasia, a family history of gout and a personal history of renal disease were sought initially. If these proved negative, the elevation was judged to be idiopathic. In similar studies by Hauge and Horwald,[112] they tabulated the incidence of nongouty hyperuricemia in 130 males and 150 females. Ten per cent had an elevated serum urate. There was no significant trend in males decade by decade. On the other hand, a peak was reached in females in the 60 to 69 year group. Additional data on this subject are desirable and could be obtained if the serum urate determinations were included in one or more public health screening programs.

Renal Exchange of Urates

THE CONCENTRATION OF urate in glomerular filtrate is presumed to be similar to that of a protein-free filtrate of plasma, while the concentration of urate in bladder urine may be from three to fifteen times greater The mechanism whereby the kidney removes the great quantity of water, and only slightly less of urate, from glomerular filtrate, and excretes a urine of higher urate content than that of serum is of considerable significance The determination of the rate of formation of glomerular filtrate, the initial essential function, may be measured by the clearance of inulin or manitol as described by Smith[224] A normal male with a surface area of 1 72 square meters forms approximately 125 ml of glomerular filtrate per minute as measured by this procedure. Not more than 1 or 2 per cent, however, of the total fluid in glomerular filtrate at any time finds its way into the bladder except under the influence of diuresis or other abnormal states The remaining 98 or 99 per cent is reabsorbed On the other hand, not more than one-half of the urea present in glomerular filtrate is reabsorbed under optimum conditions, the remainder is excreted. Clearance of urea, therefore, is computed as approximately one-half that of manitol clearance, or 62 ml /min The clearance by the kidney of any substance that is excreted in glomerular filtrate is calculated as the volume of plasma or serum water excreted per minute necessary to carry that quantity of the substance into the bladder The clearance datum is independent of the volume of glomerular filtrate reabsorbed by the tubules or excreted into the bladder

The clearance of urea is greater than that of most naturally occurring constituents of body fluids, presumably because of the desire of the body to rid itself of this nitrogenous end-product Urate shows a considerably lower clearance than urea and approaches that of sodium, chloride and other electrolytes Approximately 90 per cent of urate in glomerular filtrate is reabsorbed, only 10 per cent is excreted The dog, except for the Dalmatian coach hound, reabsorbs only 75 per cent of the uric acid in the glomerular filtrate Because of the negligible ability to reabsorb uric acid from glomerular filtrate the total urinary excretion of uric acid is high in the Dalmatian[49] The theory of the renal ex-

change of urate in man postulates that urates, as well as several other urinary substances, are not excreted by the tubules This presumption should be accepted as factual until evidence to the contrary is forthcoming The unique observation reported by Praetorius and Kirk [191] of a urate clearance rate in a nongouty male considerably greater than the glomerular filtration rate, has not been explained The concentration of urate in the serum was 0 6 mg 100 ml or less It is argued that in this subject the uric acid was excreted by tubular secretion or that uric acid was formed by the kidney

In several laboratories, investigations to determine urate clearance in gouty and nongouty subjects agree generally in their results The urate clearance of most gouty patients, irrespective of the stage of the disease, parallels closely that of nongouty controls, i e, approximately 10 ml /min [56] It is interesting to note that only a slight depression of urate clearance in the case of gouty patients occurs with a significant depression in glomerular filtration rate and with demonstrable nitrogen retention Urate clearance tends to be maintained at the expense of per cent resorption as glomerular filtration rate is impaired by progressive renal damage These observations furnish additional support to the contention discussed in the section on *Etiology*, i e , that kidneys of gouty patients show no differential ability to clear urate

Berliner and associates [20] have extended these observations and have investigated the possible role of a tubular reabsorptive capacity in regulating urate excretion and plasma urate concentration An increase in urate clearance accompanied an increase in plasma level It was apparent, however that the magnitude of the urate reabsorptive capacity is so great that it is almost certainly never saturated in the normal individual "This being the case, the Tm per se cannot be considered as *directly* involved in the regulation of the plasma urate concentration or even in the regulaton of urate excretion " It is believed that these studies on the normal are applicable to patients with gout

The paradoxic retention of uric acid by uricosuric drugs at low dosage has been restudied by Yu and Gutman [280] Salicylates, phenylbutazone, and Benemid were perfused intravenously in their investigations A slight depression in uric acid clearance occurred at

low plasma levels. These findings help clarify the discordant results regarding the uricosuric action of phenylbutazone Small doses are not associated with uric acid diuresis However, since the current tendency is to use large doses of phenylbutazone, the paradoxic retention of uric acid should not be of clinical significance. A paradoxic retention of uric acid following administration of Benemid has not been reported clinically. Such a possibility is obviated by the average dose recommended (1.0–2.0 Gm i.d).

Among the several factors that condition the solubility of urate in urine are the concentration of hydrogen ions and the concentration of sodium ions Within the physiologic range of hydrogen ion concentration, the more alkaline the urine, the greater the solubility of urate salts At a constant pH, sodium ions depress urate solubility It has been calculated that approximately 100 mg of uric acid would be held in solution if there were sufficient sodium ions present to form a saturated solution of sodium urate at pH 6.9. The observations on gouty subjects agree with the theoretic calculations A solubility greater than 100 mg /100 ml. in the urine of gouty patients has been observed [247] A number of gouty patients on a low purine diet excrete urates in a concentration varying between 50 and 100 mg /100 ml Others excrete a urine with a lower concentration. This then does not appear to be a function of depression of renal impairment, but may be related to the size of the metabolic pool The belief by Thannhauser [250] that patients with gout could not concentrate urates above 60 mg./100 ml. has not been confirmed by these experimental observations.

The total excretion of uric acid per day by gouty patients may be of considerable magnitude Normal controls on a low purine diet will excrete from 300 to 500 mg /24 hours Many gouty patients, irrespective of the stage of the disease, will excrete a somewhat greater amount A few patients will excrete more than 1000 mg /24 hours There are instances recorded of patients excreting more than 2000 mg per day Friedman and Byers [82] have reinvestigated this subject and have stressed the importance of collecting observations from young gouty subjects The average daily excretion on a purine-free diet for several young nongouty controls was 390 mg of urate The average for four young gouty patients was 567 mg on a similar diet It should also be noted that the average maximum urinary

concentration of urate in the normals was 44 mg while in the young gouty patients it was 68 mg/100 ml Also, three of the five gouty patients in one or more 24-hour urine samples showed a concentration greater than 75 mg/100 ml One of the earliest qualitative observations of a urine of high urate content was recorded by Gairdner.[85] "The urine [in gout] is much diminished in quantity, and readily deposits a crust of urates on the vessel which receives it This amorphous deposit consists of urate of ammonia with urates of soda and lime. Its extreme insolubility leads me to believe that it sometimes, at least, contains pure uric acid I have frequently thrown on it vast quantities of water, both hot and cold, without in any degree affecting it Housemaids, too, well know that in such cases the knife alone will remove it "

The excretion of urates by the kidney may be modified by the action of each of the several anti-arthritic agents except colchicine Salicylates were the first class of substances to be identified with uricosuric properties This observation was reported by See[214] in 1877 and confirmed by Campbell[50], the latter also noted the absence of any demonstrable effect of colchicine upon urate excretion Some time later it was discovered that cinchophen had a similar uricosuric effect[181] No experimental data suggest that either salicylates or cinchophen affect urate excretion by altering the intermediary metabolism of purine substances Neither is there an appreciable increase in amount of urates filtered by the glomerulus nor any change in permeability of the glomerular membrane for passage of urate The effect is believed to be the depression of the quantity of urate resorbed from glomerular filtrate with a concomitant increased excretion in bladder urine Salicylates are excreted by tubular cells which show a particular affinity for benzoic acid ring compounds and become actively concerned in removing them from the blood following their ingestion If tubular cells are busy removing salicylates from the blood, they appear to be less efficient in reabsorbing urates, and so an increase in urate clearance results

There are a number of other agents that alter urate exchange by the kidney (TABLE 2) Diodrast (3 5 diiodo-4-pyridon-N-acetic acid diethanolamine) is an effective agent in increasing urate clearance[240] At high plasma Diodrast levels the urate clearance may be increased fivefold High blood glucose levels likewise may result in

TABLE 2 *Action of Drugs upon Urate Clearance*

DESCRIPTION	SERUM CONCENTRATION *mg /100 ml*	SERUM URATE *mg /100 ml*	URATE CLEARANCE *ml plasma cleared/min*	URATE REABSORPTION *per cent*	GLOMERULAR FILTRATION RATE *ml plasma/min*
Phenylbutazone	12 5	4 3	11	89	96
G 25671	13 4	7 0	50 7	56	115
Probenecid	5 0	5 0	20	82	110
Diodrast	46	6 1	49	2	50
Diodrast	1 7	10 7	30	62	80
Glucose	440	3 1	56	13	63
Sodium Salicylate		8 8	35	48	67
Salyrgan		11 0	33	52	69
Cinchophen		6 0	18	76	74
Colchicine		6 9	11	86	80
Mannitol	440	8 6	8	89	72

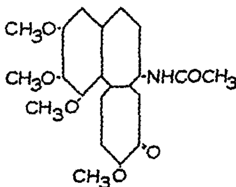
a significant increase in urate clearance Neither of these uricosuric agents is practical in maintenance therapy Diodrast must be administered intravenously with the resultant action persisting for only a few hours, while the concentration of glucose in the blood must be increased to 400 mg./100 ml or greater to produce a uricosuric effect similar to that of Diodrast Recently the uricosuric action of ethyl biscoumacetate has been demonstrated by Sougin Mishbashan and Horwitz [232] Following the oral administration of 1 0 Gm of the active material, an eightfold increase in urate clearance with a diminution in concentration of urate in the serum was observed This is an interesting experimental observation but at the present time has no clinical implications for victims of gout The authors note that ethyl biscoumacetate is not the first compound with a combined uricosuric and anticoagulant property Salicylates and cinchophen may impair prothrombin activity as well as influence excretion of uric acid

In recent years, two anti-gout drugs have become available for the specific purpose of enhancing urate excretion Phenylbutazone has been investigated in several laboratories and found to be endowed with measurable uricosuric properties When given intravenously, there may be a threefold increase in urate clearance [232] Oral administration of the drug has a less dramatic action Nor do all patients with gout show an increase in urate clearance with oral phenylbutazone The last uricosuric drug to be mentioned and the most effective is probenecid (Benemid) Its use in the intercritical period is of great clinical value and will be discussed extensively in the section on *Treatment* The alteration of urate exchange is pertinent to this section This is an effective uricosuric agent in doses ranging from 1 to 2 Gm daily A significant increase in excretion of uric acid in the urine and a concomitant decrease of uric acid in the serum has been a reproducible observation The site of action is believed to be the tubular cells in the kidney, similar to salicylates and phenylbutazone, and no alteration of the intermediary metabolism of uric acid or purine substances has been demonstrated

——Pharmacology of Anti-Gout Drugs——

Colchicine:

COLCHICINE, ONE OF THE oldest drugs in the pharmacopeia, remains an enigma to the pharmacologist and defies interpretation of its clinical action, by the physician. Colchicine is present in at least 64 species of plants of the genus *Colchicum linnaeus* Many of the species may be grown in the Northern Hemisphere but each is indigenous to the Mediterranean region[69] The presumptive structural formula of colchicine, as proposed by Windaus, is no longer accepted. The probable structure is as follows:



Colchicine is the active principle of the wine or tincture of colchicum and should be used exclusively. Because of the variability in their potency, colchicum preparations are unreliable in their action Crystalline colchicine is available currently as the tablet or granule, 0.5 mg or 0.6 mg (1/120 or 1/100 grain). Why there should be two preparations of similar strength in general use is impossible for me to understand.

The use of colchicine in gout is empirical, and the mechanism of the anti-articular action is unknown. Not being an analgesic, it does not relieve other types of pain or inflammation and is of no value in other types of arthritis.[154] There are, however, several clinical references to the contrary in the monograph by Haden[103] published in 1820 entitled: "Practical Observations on the Colchicum Autumnale, as a General Remedy of Great Power, in the Treatment of Inflammatory Diseases Both Acute and Chronic; and

Therefore as a Substitute for Bleeding, in Disorders Which are Connected with Increased Action of the Heart and Arteries"

One instance concerns the "*Case of Inflammatory Fever in a Horse*"

> "In August, 1820, a horse of my father's went a journey of 500 miles He was occasionally unwell at the latter part of the journey, but was not laid up, until he had been ailing for a week in the early part of September .. His legs and joints generally became stiff and very much swelled, and his difficulty of breathing increased, until it appeared necessary to take away three quarts of blood Colchicum was now given to him in the dose of two drachms every six hours The medicine was continued for two days, when his symptoms were nearly gone, his joints had almost acquired their natural size, and the horse was more lively Because he was much purged, laudanum ℥ss, and comp tincture of gentian ℥ii were given, and on the next day he was perfectly in a state of convalescence, and the swelling of his joints being completely relieved"

Colchicine is neither a diuretic nor a uricosuric agent Gairdner[85] maintained that the beneficial action of colchicine was not related to an increased excretion of urinary urates, a conclusion still valid In the initial studies employing N^{15} isotopes in this laboratory, it was believed that colchicine might decrease the magnitude of the miscible pool of uric acid[244] It is believed now that these original observations were not valid Colchicine has gained considerable fame in recent years because of its action upon mitosis in plants[44] In order to produce this effect, it is necessary to give, per unit mass of experimental material, approximately 100 times the therapeutic dose recommended for gouty patients Suffice it to say, we do not need to concern ourselves about inducing cancer by the oral administration of colchicine if therapeutic amounts only are recommended The gastrointestinal tract rebels when the therapeutic limit is exceeded by even a few tablets Nor have we observed an increased incidence of cancer or other malignant tumors that could be attributed to colchicine in patients who have received therapeutic quantities of the drug daily over a period of many years In several species of mammals, including man, colchicine produces a temporary leukopenia which is soon replaced by a leukocytosis This action is associated with an increase in the number of basophilic granulocytes Toxic amounts of colchicine may cause a granulocytosis or an aplastic anemia, but these amounts also far exceed the therapeutic quantities suggested for the control

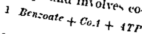
of acute or chronic gouty arthritis Due to the ability of colchicine to arrest mitosis, it has been employed in acute and chronic leukemia, but with results not particularly encouraging. The same may be said for the administration to patients with carcinoma

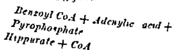
The side effects of excess colchicine intake usually are confined to the gastrointestinal tract Abdominal pain, nausea and vomiting are characteristic If ingestion is continued beyond this point, loss of fluid and electrolytes from the body may be critical Fat nephrosis has been produced experimentally in animals with large amounts of the drug Ominous gastroenteritis and intestinal bleeding have been reported by Davis[62] and Shanbrom[217] following administration of therapeutic quantities of colchicine to patients with complicated gout Bronsky and Bernstein[42] observed a similar untoward effect in a patient with multiple myeloma who developed one acute articular episode A total of 10 2 mg of colchicine was administered over a period of 36 hours This is a rather large amount for a 68 year old person with as serious a malady as multiple myeloma We have not seen either side effect in our experience

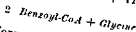
Probenecid (Benemid)

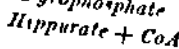
The synthesis of Benemid (p-(di-n-propylsulfamyl)-benzoic acid) as a uricosuric compound followed the observation of Wolfson and associates[271] that carinamide, a parent substance, inhibited reabsorption of uric acid The daily requirements of from 18 to 24 Gm of carinamide in order to obtain uricosuric effects of clinical significance prompted the search for a more potent preparation As a result of a review of a number of compounds in the pharmacology laboratory, probenecid was selected because of its effectiveness in altering tubular exchange as well as for its low toxicity Probenecid alters the renal exchange of penicillin, uric acid, p-aminosalicylic acid and p-aminohippuric acid and inhibits the conjugation of glycine and benzoic acid[22]

The conjugation of benzoic acid and related compounds occurs in two steps and involves co-enzyme A as follows.[91]


1 *Benzoate + CoA + ATP*


Benzoyl CoA + Adenylic acid + Pyrophosphate


2 *Benzoyl-CoA + Glycine*


Hippurate + CoA

The formation of an activated benzoate, namely, benzoyl-CoA and the enzyme for this reaction, is provided by ATP (adenine tri-

phosphate). Action 2, is a transfer of the benzoyl group from CoA to glycine[207] Benemid has been shown to compete effectively with benzoate in the activation reaction but has no effect upon the subsequent transfer to glycine It has been postulated that the intermediate compound in the renal transport of penicillin and related substances is the CoA complex Benemid interferes with the transport by forming a complex with CoA that is less dissociable than that of penicillin The cellular mechanisms for uric acid transport and the manner in which they are inhibited by Benemid are com-

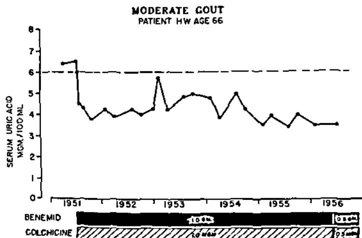


FIG 7 Experimental observations on a 66 year old male with moderate gout who has responded well to colchicine and Benemid prescribed daily There have been no attacks of gout since the colchicine Benemid regimen was begun in 1951

pletely unknown even though the mechanism described above is applicable to penicillin Benemid does not affect the urinary excretion of any known important endogenous substance other than uric acid and affects in no way the other electrolytes handled by the kidneys[222] A modest diuresis with an increased urinary excretion of sodium and chloride has been observed in nongouty edematous persons[42] Benemid lacks any analgesic properties, does not enhance any of the anti-gout agents during the acute attack and is not a cure for the malady The combination with colchicine is highly effective, however, in the prophylaxis of acute attacks

The beneficial action of Benemid in patients with gout has been well documented and the prophylactic value confirmed, as will be discussed in the section on *Treatment*. Rapidly and effectively absorbed from the gastrointestinal tract, it is carried in the blood stream partially bound by plasma protein. The unbound portion gains access to the glomerular filtrate but is largely resorbed by the renal tubules. The blocking action of Benemid may be apparent within a few hours after beginning ingestion. It is associated with an increased excretion of uric acid in the urine, a decreased concentration of uric acid in the serum (FIG 7), and a decrease in the metabolic pool so long as daily ingestion is continued. The effect upon the serum during the first few days may be greater than that observed subsequently, but at no time is it abolished, and in

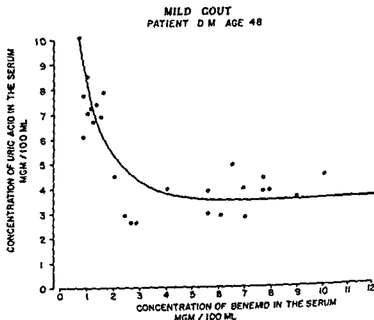


FIG 8 Concentration of serum uric acid as a function of serum Benemid content. The observations were collected over a period of three years.

most patients, the action upon the several functions may be demonstrated so long as the drug is administered daily. The depression of serum urate is a function of concentration of Benemid in the

serum (FIG 8) over the range 0 to 5 mg /100 ml. of Benemid Thereafter, higher concentrations of Benemid exert a negligible effect upon serum urate.

The uricosuric action of Benemid may be nullified, totally or partially, by the simultaneous administration of salicylates. Pascale and associates[185] noted that 5 2 Gm. of acetylsalicylic acid completely suppressed the uricosuric action of 2 0 Gm of Benemid Because of this antagonistic action, salicylates should not be prescribed during the Benemid regimen Also the excretion of phenolsulfonphthalein is inhibited by the renal tubules under the influence of Benemid[31]

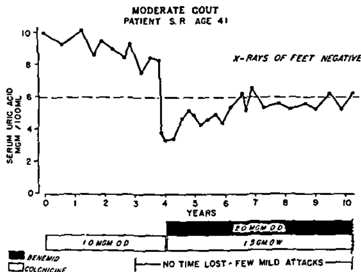


FIG 9 Serum urate concentrations in patient S R, during the past decade Although he is a sufferer from moderately severe gouty arthritis, there have been no days lost from work for more than six years

During the more than six years' use of Benemid in our clinic, the beneficial effects have persisted Selected data from S R are given in FIGURE 9 *This patient has been followed for approximately* ten years and has been on Benemid for more than six years In the pre-Benemid era, the concentration of uric acid in the serum was determined several times and varied between 7 6 and 10 5 mg /100

TABLE 3. *Experimental Observations on Three Patients with Gout following Phenylbutazone and Benemid*

PATIENT	STATUS	MISCIBLE POOL URIC ACID *mMol*	TURNOVER RATE *Pools/Day*	SERUM URIC ACID *Mg /100 ml*	URINE URIC ACID *mMol /24 hrs*
D P	Control	61	0.30	8.3	11.8
	Phenylbutazone	56	0.47	6.3	16.3
	Probenecid	63	0.32	6.9	18.9
M B.	Control	55	0.41	11.1	7.7
	Phenylbutazone	41	0.54	10.8	10.1
	Probenecid	41	0.51	7.9	14.9
M F.	Control	57	0.70	11.0	16.6
	Phenylbutazone	35	0.92	8.0	13.1
	Probenecid	36	0.98	5.3	30.7

receiving Benemid, the course of the former should be a relatively short one.

Precipitation of acute attacks of gout following the institution of Benemid appeared to us to be as real a threat in the early experimental period as did the development of renal stones. Subsequently, this fear has not been substantiated. No longer is it our practice to caution patients of the possibility of an acute attack developing as a result of Benemid intake. Clinical experience has revealed that the incidence of acute exacerbations during the first few months of Benemid, with full doses of the drug, is slightly less than in the pre-Benemid period. If smaller doses are given initially and later increased, the incidence of acute attacks is not a clinical problem. This statement assumes that colchicine is taken together with Benemid, as described in the section on *Treatment*.

Phenylbutazone (Butazolidin)

Phenylbutazone (3,5-dioxo-1, 2-diphenyl-4-n-butyl-pyrazolidin sodium), a congener of aminopyrine and antipyrine, is an excellent analgesic as well as an anti-inflammatory agent. Unlike salicylates, another analgesic-antipyretic agent, phenylbutazone does not stimulate pituitary-adrenal hormones, as evaluated by animal experiments.[131] A secondary effect is the decrease in concentration of serum uric acid and, in some experiments, an increased urinary excretion of uric acid. With an average daily dose of 1.0 Gm. of phenylbutazone, Johnson and associates[131] observed a decrease in serum concentration from 8.6 to 5.5 mg./100 ml. in sixteen patients. The effect upon the urinary excretion of uric acid is of a lower order of magnitude than Benemid,[156] and the results less predictable. Bishop and associates[26] investigated urate clearance in three patients with gout and four patients with rheumatoid arthritis who served as controls. Two of the three gouty patients exhibited a uricosuric effect with phenylbutazone but only one of the four patients did so with rheumatoid arthritis. Alterations of the metabolic pool of uric acid as a function of phenylbutazone intake has been studied in these patients also. Two of the three patients with gout and three of the four controls (TABLE 3) showed a reduction.[26] Huffman and associates[124] observed that uricosuria was present only if the serum phenylbutazone levels exceeded 10 mg./100 ml. A daily intake of 600 mg. or more of the drug was necessary to achieve such

a concentration in the serum. Three patients in the study demonstrated a decreased 24-hour urate excretion in spite of a decrease in serum urate concentration The marked fluid retention was believed to be responsible for the serum urate decrease. Wyngaarden[276] observed similar discordant results in two normal individuals One subject showed an increased excretion of urate with an intake of 800 mg of phenylbutazone daily, the response in the second patient was minimal The serum urate concentration fell in each experiment Retention of fluid and expansion of extracellular fluid volume is the untoward action responsible.

Cardiac decompensation and acute pulmonary edema have been observed following administration of phenylbutazone This dire action is not surprising, since the plasma volume may be increased by 50 per cent Untoward effects of sufficient severity to warrant discontinuing medication are observed in a significant number of patients.[144] In addition to water and salt retention, the undesirable effects include nausea, vomiting, gastrointestinal discomfort and skin rashes Vertigo, insomnia, nervousness, hematuria, blurring of vision, hepatitis and a decrease in radioiodine uptake by the thyroid have been observed The incidence of peptic ulcer following prolonged phenylbutazone therapy is appreciable, and agranulocytosis and death from aplastic anemia has occurred Phenylbutazone may be useful in the management of the acute attack of gouty arthritis, but it is believed that its use is contraindicated in long-term management.

4-(Phenylthioethyl) 1, 2-Diphenyl 3, 5-Pyrazolidinedone (G-25671, a phenylbutazone analog)

This compound, a potent uricosuric agent when injected intravenously, has been studied in Gutman's laboratory.[291] Urate clearances as high as 50 ml./min were observed with minimal changes only in the serum urate level. Glomerular filtration rate was not altered There was less sodium and water retention than has been observed following administration of phenylbutazone. Oral administration of 1 0 to 2 0 Gm., daily, resulted in a significant decrease in serum urate and an increase in urinary uric acid comparable to Benemid The uricosuric action in patients with renal sufficiency was less satisfactory. The potential toxicity is the limiting factor in the treatment of chronic gouty arthritis

Salicylates

Acetylsalicylic acid and sodium salicylate have long been recognized as anti-gout agents The name aspirin, from "spirsaure," German for salicylic acid, was introduced into clinical medicine at the end of the nineteenth century The analgesic action of the salicylates comprises the principal value in clinical medicine The uricosuric acid action has received considerably less attention, especially in this country On the other hand, as noted in the section on *Treatment*, Marson[166] in England has placed considerable emphasis upon the uricosuric and tophi-shrinking properties of subtoxic doses of sodium salicylate An interesting clinical observation associated with the employment of this agent in England has been reported by Kersley and associates[135] Four of a total of thirteen gout patients developed an acute attack of gout within 72 hours following termination of an experimental period on sodium salicylate Eight grams had been administered daily for three days only

Adrenal Steroids

Adrenocorticotropic hormone (ACTH) and the adrenocorticosteroids have enjoyed varying degrees of popularity in the management of the gouty patient Cortisone and adrenocorticotropin were the preparations originally used in the treatment of acute gouty arthritis Later, hydrocortisone was available for oral and intra-articular use Recently, prednisone and prednisolone have become popular None of these preparations is recommended for long-term therapy, and any merit resides in their use for acute symptoms only in selected instances The immediate pharmacologic actions, therefore, will be the only ones described Although considerable emphasis has been placed upon the influence of these preparations on the target cells, the general supportive action is probably equal to any specific target cell effect in relief of symptoms associated with the acute attack The action of the steroids upon carbohydrate, protein and fat metabolism and alteration of the electrolytes and water are not vital in the acute experiment The antipyretic, euphoric and anti-inflammatory actions of the steroids undoubtedly account for their major value Although a slight increase in excretion of uric acid in the urine may follow the adminis-

tration of any one of these preparations, it is not believed that this action per se contributes significantly to the therapeutic result. In the order of efficiency, I believe that ACTH is the best of the steroids in the treatment of the acute exacerbation Next in order I would place intra-articular hydrocortisone, followed by the other steroids without preference The phenomenon of precipitation of acute attacks following withdrawal of ACTH should be appreciated This reaction may be avoided by continued administration of colchicine, which should be fundamental in the management of the acute attack, as will be noted later

Pathology

THE CHARACTERISTIC PATHOLOGIC feature of gouty arthritis is the deposition of monosodium urate—monohydrate



$$(Na\ (C_5H_3O_3N_4) \cdot H_2O)$$

in articular and periarticular structures, especially in the peripheral joints of the extremities Despite any proof, I believe that deposition of urate in joints precedes clinical symptoms of acute gouty arthritis Recurring deposition of microscopic amounts of urate may continue for years before tophi are demonstrable grossly A relationship between the initial deposition of urates in articular structures and an increased concentration of this substance in synovial fluid, approximating the concentration in a protein-free filtrate of plasma, may be suspected. The fact that the earliest findings observed upon microscopic examination of articular cartilage are the deposits of urate in the upper layer suggests a migration of urates from synovial fluid rather than from the capillaries in the osseous structures [180]

Duckworth [67] was the first to demonstrate urate crystals projecting into the matrix of the cartilage perpendicular to the joint surface. This observation, together with the finding of a synovitis, convinced Pommer [191, 192] as well as his successor, Lang,[145] that the initiating process probably was in the joint cavity and that deposits of urates in the cartilage followed Minor trauma to a portion of the

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cartilage may be sufficient stimulus to initiate the process. Once the microscopic tophus is formed, additional precipitation of urates may follow a physical-chemical pattern similar to the salting out of a substance from a supersaturated solution Opposed to this theory were the conclusions of Ebstein[68] and Brogsitter,[40] who conceived of a reverse path, i e, urate crystals migrating from the epiphysis to the articular surface There has been considerable discussion also regarding a tropism of articular cartilage for urate salts Ebstein[68] championed the theory that focal necrosis antedated the precipitation of urates We favor the explanation offered by Pommer, since the pathologic examination of the cartilage in gouty patients reveals deposition of urates without associated necrosis *Another argument against the focal necrosis theory is the unlikelihood* of a necrotizing process responsible for such widely disseminated trauma developing progressively over a period of many years

Urate deposits are prone to develop in avascular, rather than in vascular tissue[238] The predilection for cartilage, epiphyseal portions of bone, synovial membrane, bursae, ligaments and tendons is responsible for articular complaints (PLATE III) Those severely afflicted may be riddled by urate tophi in these several structures Once the process has started in the joints, the tendency to precipitation of urates in subcutaneous spaces about the joints is enhanced (PLATE IV) Soft tissues some distance removed from the vulnerable structures rarely are involved except for the kidneys[218] Tophi are conspicuously absent from muscle, liver, spleen, lungs and nervous tissue There are, however, a number of isolated cases in which uric acid deposits have been recovered and identified chemically in atypical areas of the body These include the eye,[266, 278] the corpus cavernosum and prepuce of the penis,[84] tongue epiglottis, vocal cords, arytenoid cartilage,[11] the aortic valve[58] the mitral valve[40, 253] and the myocardium[114]

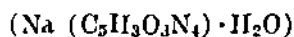
Articular Structures

The gross appearance of a gouty joint depends upon the age of the patient and the duration and severity of the articular disease. A joint in a young or middle-aged person which has been the site of only a few acute attacks of gout may show little save for a few microscopic urate deposits As the deposits spread over a larger area

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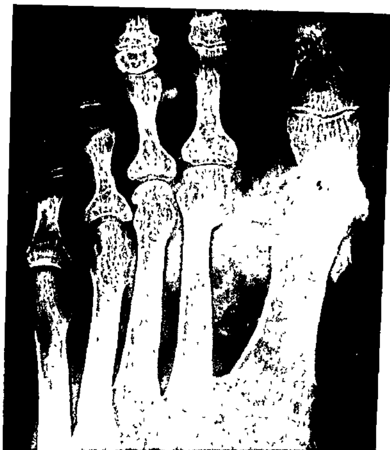


FIG. 10 Roentgenogram of the left foot of S G., a 46 year old male with a 22 year history of extensive gouty arthritis A cousin was similarly afflicted There was evidence of nitrogen retention. The concentration of uric acid in the serum was as high as 12 3 mg /100 ml The patient responded well to the colchicine Benemid regimen over a period of more than four years Fusion of the metatarsal phalangeal joints of the great toe and a urate tophus in the soft tissues are illustrated. There is some increase in calcified material about the bunion joint

during the progress of the malady, they may finally cover the articular cartilage There may be lipping and grooving in older persons, evidence of degenerative joint disease *In an advanced case of gout,*

irrespective of the age of the patient, urate deposits may be intermingled with structural changes of degenerative joint disease and, in other areas, with changes similar to those observed in rheumatoid arthritis. This fact has led some clinicians and radiologists to designate gouty arthritis as a "mixed" type of arthritis. This synovial membrane may hypertrophy, and extensive erosion and destruction of cartilage may be followed in some instances by fibrous ankylosis or by bony ankylosis (FIG 10).

Calcium deposits have been noted infrequently in soft tissues (PLATE V) following prolonged urate deposition (FIG 11), they may be detected also in the cartilage of an affected joint[150]. Abnormalities caused by urate deposition in gouty joints usually are associated with absorption and not deposition of calcium salts. The exostoses, considered to be characteristic of degenerative joint disease, are associated with calcium deposition but are not believed to be an integral part of the pathological alterations in gouty joints.

The material selected for microscopic examination must be prepared with special care by a laborious and painstaking technique if urate crystals are to be demonstrated (PLATE VI). A nonaqueous solution is preferred for the fixation of specimens since urates are soluble in water. Absolute alcohol serves this purpose well. The cartilage cells lose their normal appearance following infiltration with urates and subsequently are replaced by this substance as the invasion from the superficial layers proceeds. Gradual progression of urate infiltration causes large portions of cartilage to be involved with the resulting development of clefts and irregularities. The cartilage stains poorly, may be fibrillated and the lacunae often contain large numbers of cells. Other portions of the diseased cartilage may be covered by a fibrous pannus arising from the synovial membrane. At the junction with the articular cartilage, the proliferating synovial membrane appears beneath the cartilage with destruction as well as thickening and pannus formation over the cartilage[215]. In location and superficial appearance, the pannus does not differ from that seen in rheumatoid arthritis except for the deposits of urates. The pannus may cover the entire cartilaginous structure with extensive urate encrustations[205]. Subcondral areas, medullary spaces, capsules, ligaments, tendons, bursae and other periarticular structures may be invaded eventually by urates.



FIG 11 Roentgenogram of the left foot of F M, a white male who had suffered from attacks of arthritis since the age of 6. He died at the age of 36. He was the most severely afflicted case of chronic tophaceous gout in our series Many toes and fingers were amputated over a period of twenty years Massive urate deposits were present in all of the extremities together with extensive calcium deposits (See PLATE X)

Periarticular tophi are composed of fibroblasts, polynuclear cells, lymphocytes, plasma cells and giant cells interwoven with

urate crystals, in some instances, an intense inflammatory reaction is apparent. A soft tissue tophus may contain a core of cholesterol and other necrotic debris surrounded by urates.[59, 146] The tissue cells are crowded as the tophus enlarges and an avascular mass of urate results, eventually causing their death. The subcutaneous tophus is surrounded by a connective tissue capsule when it reaches a size that is cosmetically unattractive.

It is deemed unnecessary to postulate that urate deposits cause necrosis of bone during or after infiltration of the medullary or cortical spaces. It suffices to assume that urate deposits in apposition to bony trabeculae inhibit osteoblastic activity and that as bone is resorbed normally, it is not replaced in the immediate vicinity of a tophus. Since bone is capable of regeneration, however, it is possible with the appropriate therapeutic agents, for tophi to be resolved and normal bone architecture restored. This series of events probably is unusual, and unfortunately, most tophi that develop in bone increase in size rather than decrease. At least, this was the inevitable sequence prior to the introduction of Benemid several years ago. Subsequent studies may furnish proof that it is possible for urate tophi to be replaced eventually by normal trabecular pattern under the persistent influence of Benemid.

Kidney Tissue

The kidneys constitute the only vital structure that frequently is affected in patients with gout. In spite of great variability in the pathologic changes in the kidney that have been reported, the severity of the morphologic alterations may be unrelated to the clinical course of the disease. The kidneys may be normal in size and weight or they may be small and atrophic and less than one third of the normal size. The capsule may strip easily or with some difficulty. The exposed surfaces may show minimal or marked scarring (PLATE VII). If urate deposition is slight, it will be evident only from a gritty sensation as the kidney is sectioned with the knife. A careful search with a dissecting microscope should be made if urate crystals are suspected but are not identified grossly. Urate deposits are visible readily upon the cut surface of the kidney

in some cases (PLATE VIII). They appear as streaks of yellow-white throughout the parenchyma but are most abundant in the medulla. In addition, the cortex and medulla may contain cysts, abscesses filled with purulent material or evidence of a healed pyelonephritis. Upon microscopic examination the structural alterations may simulate chronic glomerulonephritis, benign nephrosclerosis or pyelonephritis.[152] The glomeruli may be normal in appearance or hyalinized, partially or completely, with thickening of the intercapillary substance.[187] Blood vessels share in the extensive changes.[43] The collecting tubules are dilated and loaded with urate crystals, hyaline casts and calcific concretions[150] or are atrophied and surrounded by interstitial fibrosis. The deposits of urate in the interstitium may be surrounded by an accumulation of lymphocytes and foreign body cells. An example of lower-nephron nephrosis has been described by Brown and Mallory.[43] Severe degeneration of the lower portion of the tubules, blood and pigment casts and interstitial inflammation are considered typical.

The development of amyloid changes in the kidney may follow long-standing low-grade pyelonephritis or a long-standing untreated sinus in a subcutaneous tophi (PLATE IX). Patient A C, a white male, died at the age of 72 of coronary heart disease and uremia. He had suffered attacks of acute gouty arthritis since the age of 35. For more than a decade he had discharging sinuses from urate tophi on the lateral aspect of each foot. There was only a trace of albumin in the urine, and the specific gravity was as high as 1.028. At postmortem examination, all of the glomeruli showed intercapillary deposits of amyloid. There were also deposits of uric acid crystals in the medullary areas.

There is lack of agreement regarding the mechanism of development of the diverse pathologic patterns in the kidneys. The increased concentration of urate in tubular urine provides a serious threat to precipitation, which is not amenable to control. Chemical insult to the kidney follows. Such a kidney, with urate crystals blocking the tubules initially and infiltrating the interstitium later, is susceptible to infection and pyelonephritis. Gouty patients also show an increased incidence of large vessel sclerosis and hypertension, which may be reflected in the vascular findings of the kidney.

Hence, vascular nephritis may be considered a satisfactory diagnosis at the pathologic examination in some instances Modern and Neister[175] have discussed the "gouty kidney" recently, and believe that certain clinical characteristics distinguish it from other types of kidney dysfunction The findings as tabulated include a fixed specific gravity of the urine, azotemia, absence of elevation of blood pressure, minimal or absence of proteinuria and minimal excretion of formed urinary elements, respectively The pathologic process is thought to be ascending due to compression of the collecting tubules from urate deposits Atrophy of the nephron which the tubules subserve follows eventually Such a passive process explains the absence of albuminuria and cylindruria as well as the slow rate of development of azotemia I do not believe that the lesion is as specific pathologically as described by Modern and Meister, and the total clinical characteristics are present in but a small percentage of patients with gout Thus, most of the patients in our series show a normal concentration of urea nitrogen, not azotemia, an elevation of blood pressure may be observed in a significant number, and proteinuria is a frequent finding in patients whose prognosis is not ominous

——Pathogenesis of Acute Symptoms——

THE PHENOMENON OF the acute articular episode in gout is not understood The various speculations regarding the pathogenesis of urate deposition have been discussed in the section on *Pathology* Presumably urate infiltration of joint structures precedes acute articular symptoms Zevely and associates[283] have reported microscopic findings of knee joint biopsy that support this presumption One patient, an 80 year old male, subjected to biopsy at the time of the first attack of acute gouty arthritis, showed collections of urate deposits in the synovial membrane without other evidence of tophaceous gout Once joint structures have been invaded by urates, they are never immune to an acute attack Why uric acid is deposited in relatively avascular tissues has not been determined Increased

precipitation of urate crystals during an acute attack may occur, but this supposition lacks proof Because of the polyarticular nature of many of the episodes, possibly a systemic disturbance, not an exclusively local one, should be held responsible.

Brogsitter[39] believed that the rupture into a joint space of a urate deposit in the outer layer of cartilage precipitates and precedes an acute attack The clinical symptoms of the acute attack could then be associated with the reaction of the joint to this insult. Such an explanation seems unlikely in the case of an individual with migratory polyarthritis, in the untreated individual who suffers a long bout of gouty arthritis, or in one who suffers repeated attacks in the same joint If a burst of uric acid crystals into the joint space were responsible, the concentration of uric acid in the synovial fluid during the acute attack might be considerably above that observed at other times The concentration of uric acid in the synovial fluid is similar to that of a protein-free filtrate, and no highly saturated synovial fluid has been recovered upon aspiration[240] Except for secondary changes usually attributed to inflammation about the joint, the author believes the physical appearance of the articular tissue at the time of the acute attack resembles that in the intercritical period

Several of the laboratory procedures that reflect acute inflammatory activity associated with rheumatoid arthritis have been positive in isolated cases of gout Included are the fibrinolysin titer,[285] the concentration of serum polysaccharides,[220] the sheep erythrocyte agglutination test and the content of gamma globulins,[129] respectively Without adequate proof it is assumed that these are nonspecific reactions in acute gouty arthritis

X-ray Findings

A SIGNIFICANT PERCENTAGE of patients with a history of gout extending over a period of years may show no abnormalities in a roentgenographic study of the bony structures between attacks During the acute attack, there may be soft tissue swelling but no essential change in the hard tissues Thus, roentgenographic examination may provide no diagnostic help at the stage of the natural history of the disease when diagnostic help is most welcome Several patients in the seventh or eighth decade of life have satisfied the other diagnostic criteria for gout in the intercritical period without revealing findings by x-ray identifiable as characteristic of the well-developed case However, each patient suspected of suffering from gout should receive the benefit of roentgenographic studies, particularly of the feet, if for no other purpose than to obtain the information for the record The x-ray films reproduced in this monograph illustrate morbid changes, and normal films are not shown The proportion of involved joints to normal joints in a series of gouty patients is not truly representative, therefore, in this presentation

The changes that may be observed in the roentgenograms of the extremities are confirmatory at times, at other times, they are nonspecific [168, 205] The metatarsal-phalangeal joint of the great toe is one of the first structures to show chronic changes by x-ray In FIGURE 12, narrowing of the metatarsal-phalangeal joint of the great toe with minimal bony overgrowth at the margins is noted There is minimal decreased density of the mid-portion of the head of the first metatarsal adjacent to the joint space The magnified x-ray films of the left foot are shown in FIGURE 13 A small lesion breaking through the medial cortex of the head of the first metatarsal almost certainly is a tophaceous deposit Minimal changes are illustrated also in FIGURES 14 AND 15 In FIGURE 16 a somewhat larger tophus is illustrated in the metatarsal-phalangeal joint of the great toe Roentgenograms of the opposing foot in this patient were negative An example of several tophi in the great toe is illustrated in FIGURE 17 Changes present in both feet are more advanced on the right and involve particularly the head of the proximal phalanx of the great toe A destructive process involving the major portion of the

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X-ray Findings

A SIGNIFICANT PERCENTAGE of patients with a history of gout extending over a period of years may show no abnormalities in a roentgenographic study of the bony structures between attacks. During the acute attack, there may be soft tissue swelling but no essential change in the hard tissues. Thus, roentgenographic examination may provide no diagnostic help at the stage of the natural history of the disease when diagnostic help is most welcome. Several patients in the seventh or eighth decade of life have satisfied the other diagnostic criteria for gout in the intercritical period without revealing findings by x-ray identifiable as characteristic of the well-developed case. However, each patient suspected of suffering from gout should receive the benefit of roentgenographic studies, particularly of the feet, if for no other purpose than to obtain the information for the record. The x-ray films reproduced in this monograph illustrate morbid changes, and normal films are not shown. The proportion of involved joints to normal joints in a series of gouty patients is not truly representative, therefore, in this presentation.

The changes that may be observed in the roentgenograms of the extremities are confirmatory at times, at other times, they are nonspecific.[164, 205] The metatarsal-phalangeal joint of the great toe is one of the first structures to show chronic changes by x-ray. In FIGURE 12, narrowing of the metatarsal-phalangeal joint of the great toe with minimal bony overgrowth at the margins is noted. There is minimal decreased density of the mid-portion of the head of the first metatarsal adjacent to the joint space. The magnified x-ray films of the left foot are shown in FIGURE 13. A small lesion breaking through the medial cortex of the head of the first metatarsal almost certainly is a tophaceous deposit. Minimal changes are illustrated also in FIGURES 14 AND 15. In FIGURE 16 a somewhat larger tophus is illustrated in the metatarsal-phalangeal joint of the great toe. Roentgenograms of the opposing foot in this patient were negative. An example of several tophi in the great toe is illustrated in FIGURE 17. Changes present in both feet are more advanced on the right and involve particularly the head of the proximal phalanx of the great toe. A destructive process involving the major portion of the

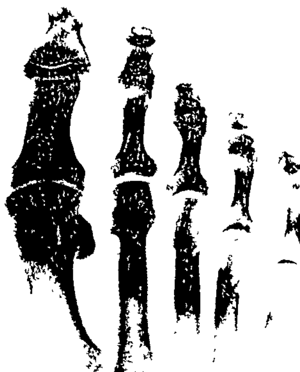


FIG 12 Roentgenogram of the right foot of W B, a 52 year old male who has suffered from gouty arthritis for more than twenty years Many of the joints of the hands and the feet are involved symptomatically Colchicine and Benemid have been taken for slightly more than eighteen months. This has resulted in the best year since 1940. There is narrowing of the metatarsal-phalangeal joint space of the great toe, with minimal bony overgrowth at the margins There is minimal decreased density in the mid portion of the head of the first metatarsal adjacent to the joint space

shaft of the middle phalanx of the fourth toe is shown in FIGURE 18 On physical examination of this member, a discharging urate sinus was apparent There is also soft tissue swelling in the region of the interphalangeal joints of that great toe with areas of destruction on the opposing margins medially

The characteristic finding in the gouty joint represents circular

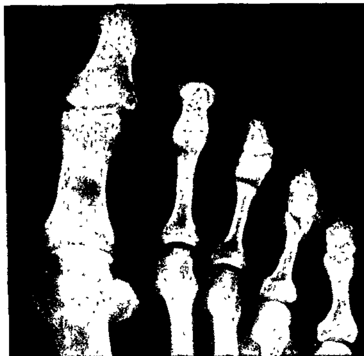


Fig 13. Roentgenogram of the right foot of W C, a 42 year old male who had experienced symptoms of distress in the feet for only two months when first seen The concentration of uric acid in the serum was 6.0 mg /100 ml X ray films of the left foot were negative A small lesion breaking through the medial cortex of the head of the first metatarsal opposite the sesamoid bones, believed to be a tophus is illustrated

or oval areas of decreased density, areas of rarifaction In some instances, the tophus appears to be unilocular and of the same density throughout In other joints, the appearance of smaller and larger tophi superimposed is created The periphery of the bony tophus usually is distinct and sharply defined A tophus on the medial aspect of the great toe is shown in FIGURE 19 Moderately extensive changes in the hands are illustrated in FIGURES 20 AND 21, in the shoulder in FIGURE 22, elbow in FIGURE 23, the ankle in FIGURE

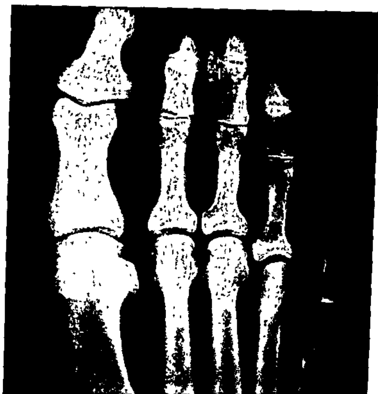


FIG 14 Roentgenogram of the right foot of F C, a 58 year old male who has suffered four attacks of acute gout, the first one in 1951 The last attack began 48 hours following extraction of a cataract from the left eye The serum uric acid was 7 4 mg /100 ml. Areas of decreased density are present in the medial and central portions of the head of the first metatarsal.

24, wrist in FIGURE 25 and patella in FIGURE 26 [159] The hand of a patient with moderately severe gout is shown in FIGURE 27, and again three years later in FIGURE 28

Demineralization of affected parts may be extensive or localized The end result of demineralization of a circumscribed area is complete replacement by sodium urate. Generalized demineralization of an affected part is a non-specific result of arthritis from disuse, not a disseminated replacement of calcium salts with urate salts



FIG 15. Roentgenogram of the left foot of same patient as in FIGURE 14. The tophus in the center of the head of the first metatarsal is well defined

Circumscribed areas of decreased density are adjacent to the articular surface originally and may involve the articular cartilage later as well as the shaft of the bone. Subsequently, there may be narrowing of the joint space and fibrous or bony ankylosis. Infrequently, there may be complete destruction of a joint with replacement of cartilage and bone by fibrous tissue and urate deposits. These advanced changes may be associated with expansion of the cortex of the epiphyseal bone, which persists as a thin shell. Extensive urate deposits, at other times, appear some distance from the articular surface with expansion of the cortex.

Deposition of calcium in a urate tophus is an unusual finding. Urate deposits exhibit essentially the same resistance to x-ray pene-

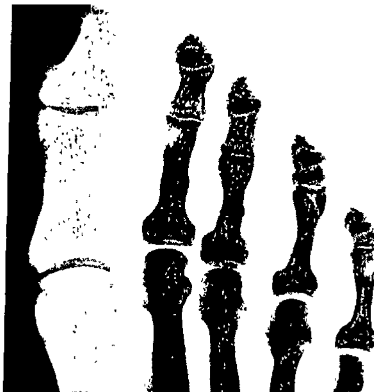


FIG 16 Roentgenogram of the right foot of a 59 year old male who has had rheumatic heart disease for more than twenty five years. For six years he has had intermittent attacks of acute gouty arthritis. The diagnosis of gout was not made until three years after joint symptoms first appeared The therapeutic response to colchicine was excellent The concentration of uric acid in the serum has been as high as 9 2 mg /100 ml An osseous tophi is present on the medial aspect of the head of the first metatarsal.

tration as the soft tissues of the body; hence they are neither radio-opaque nor radiolucent The presence of calcium in a urate tophus is of little diagnostic value In one patient calcium deposits were widely distributed in the soft tissues throughout the foot (FIG 11) All of the toes in this patient had been amputated surgically several years earlier The roentgenographic changes suggested secondary

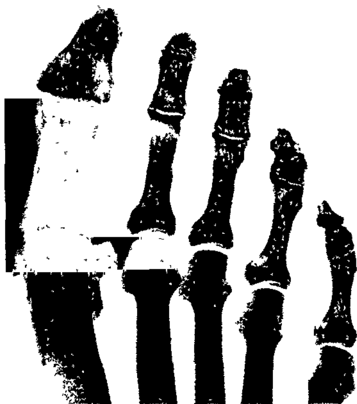


FIG 17. Roentgenogram of the right foot of a 35 year old male who has suffered intermittent attacks of acute gouty arthritis since the age of 9 Originally the symptoms were attributed to acute rheumatic fever The subsequent course suggested that gouty arthritis was responsible The family history is positive for gout The concentration of serum uric acid was 8 3 mg /100 ml Areas of decalcification are present in the head of the first metatarsal and the head of the proximal phalanx



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Fig 17 Roentgenogram of the right foot of a 35 year old male who has suffered intermittent attacks of acute gouty arthritis since the age of 9. Originally the symptoms were attributed to acute rheumatic fever. The subsequent course suggested that gouty arthritis was responsible. The family history is positive for gout. The concentration of serum uric acid was 8.3 mg/100 ml. Areas of decalcification are present in the head of the first metatarsal and the head of the proximal phalanx.



FIG 18 Roentgenogram of the left foot of a 72 year old female who had joint trouble for two decades On physical examination a sinus, discharging urates, was noted on the fourth toe The concentration of uric acid in the serum was 7 7 mg /100 ml A destructive process involving the major portion of the shaft of the middle phalanx of the fourth toe is illustrated There is also soft tissue swelling about the interphalangeal joint of the great toe with areas of destruction in the hard tissues

hyperparathyroidism or "calcium gout," but there is no relation to the uric acid disturbance under consideration and "Kalk Gicht."

The progression of changes shown by x-ray film is unpredictable It is reasonable to believe that it should be a function of the severity of the uric acid disturbance and the frequency of acute attacks of gouty arthritis Among several exceptions in our series to this postulate, patient F B is an example



FIG 19 Roentgenogram of the left foot of a 56 year old male who has suffered from gouty arthritis for more than eighteen years. He was in bed for as long as one month at a time because of acute joint distress. The concentration of uric acid in the serum was 7.9 mg/100 ml. Several tophi on the medial aspect of the great toe are evident.

The roentgenograms of the right foot of F. B., taken in 19[illegible] and shown in FIGURE 20, revealed minimal evidence of gouty arthritis and marked hallux valgus. Six years later, at the age of 84, the x rays were repeated (FIG. 20). The patient meanwhile had taken colchicine continuously and had suffered only two mild attacks during this six year period. He had not been placed on Benemid, because his gout was sufficiently mild to justify withholding this agent. The significant changes over the six year period, therefore, came somewhat as a surprise and were observed only because routine x ray examinations were done, not because of any acute distress in the feet. In contrast are the



FIG 20 Roentgenogram of the left hand of a 56 year old male who has been afflicted with intermittent attacks of gout for more than fifteen years The concentration of uric acid in the serum at the first examination was 12 mg /100 ml There were no chronic deforming changes on physical examination Several osseous tophi are present about the head of the middle metacarpal as well as narrowing of the joint space

films illustrated in FIGURES 31 AND 32, which demonstrate progression of the tophaceous deposits in some areas with healing in other areas The patient during this four-year period had been on colchicine daily and on Benemid a major portion of the time

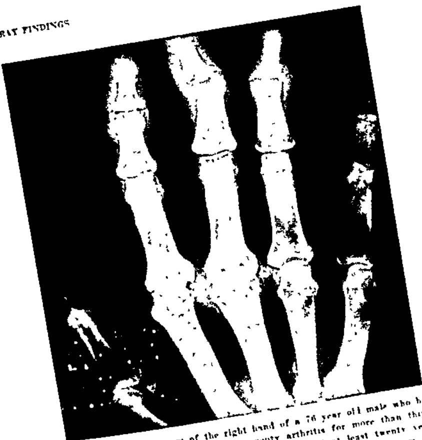


FIG 21 Roentgenogram of the right hand of a 76 year old male who had suffered intermittent attacks of acute gouty arthritis for more than thirty years The diagnosis presumably was not made until at least twenty years after the initial symptoms The concentration of uric acid in the serum was 8.6 mg /100 ml Extensive tophaceous deposits were apparent on physical examination. Many osseous tophi of varying sizes, diminution of joint space in several areas and subcutaneous deposits are illustrated There is also calcification of the arteries

In the gout studies, several anomalies each of which is probably unrelated to the metabolic dyscrasia bear comment The roentgeno-gram of the left knee of patient S.H is shown in FIGURE 11 A num-ber of attacks of acute gout had developed in this joint but th



FIG 20 Roentgenogram of the left hand of a 56 year old male who has been afflicted with intermittent attacks of gout for more than fifteen years. The concentration of uric acid in the serum at the first examination was 12 mg /100 ml. There were no chronic deforming changes on physical examination Several osseous tophi are present about the head of the middle metacarpal as well as narrowing of the joint space

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FIG 21 Roentgenogram of the right hand of a 76 year old male who had suffered intermittent attacks of acute gouty arthritis for more than thirty years The diagnosis presumably was not made until at least twenty years after the initial symptoms The concentration of uric acid in the serum was 8 6 mg /100 ml Extensive tophaceous deposits were apparent on physical examination Many osseous tophi of varying sizes, diminution of joint space in several areas and subcutaneous deposits are illustrated There is also calcification of the arteries

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FIG 22 Roentgenogram of the right shoulder of a 57 year old male who has been afflicted with acute articular distress for more than twenty-five years. There were extensive tophaceous deposits about most of the joints of the extremities Amputation of the several digits had been necessary. The concentration of uric acid in the serum was 9 8 mg /100 ml Several bony tophi in the anatomic neck are illustrated There were no tophi in the bony structures of the left shoulder

film shows osteochondritis dessicans, not osseous tophi A variation from the normal in the terminal phalangeal joint of H S. is illustrated in FIGURE 34 The possibility of a tophus was raised, but this is an unusual site for an isolated lesion The small accessory bones at the base of both distal phalangeals of the great toes and medial aspects bilaterally represent congenital variations. FIGURES 35 AND 36 are x-ray films of the feet of J G, a gouty patient. The left foot has been smaller since childhood and has not developed to the same degree as the right foot Attacks of gout have appeared without discrimination in either foot



Fig 23. Roentgenogram of the right elbow of a s tophaceous gout. The patient was placed on the colc in 1950 A striking reduction in days of incapacity (See Fig 22)



25. Roentgenogram of the wrist of a patient with extensive tophaceous
(See FIG 22)



FIG 26 Roentgenogram of the knee illustrating a large tophus in the patella



Fig 27 Roentgenogram of the hand of a patient with extensive tophaceous
(See Fig 22)



FIG. 28 Roentgenogram of the hand shown in FIGURE 27, three years later Recalcification is evident with contraction of the expanded cortex of the digits



FIG 29 Roentgenogram of the left foot of an 84 year old male who has experienced intermittent attacks of acute gouty arthritis since the age of 65 He had worked as a carpenter until the age of 76 He reported a discharging sinus several years before he was seen first The concentration of uric acid in the serum was as high as 11 2 mg /100 ml Roentgen examination of the feet in 1950 showed extensive vascular calcification, bilateral hallux valgus and minimal evidence of subchondral bone destruction characteristic of gouty arthritis

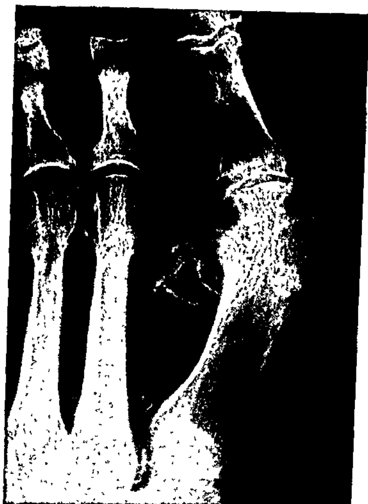


FIG. 30. Roentgenogram of the same structures illustrated in FIGURE 29, six years later. There are several punched out areas in the metatarsal phalangeal joint of the great toe, with minimal narrowing of the joint space

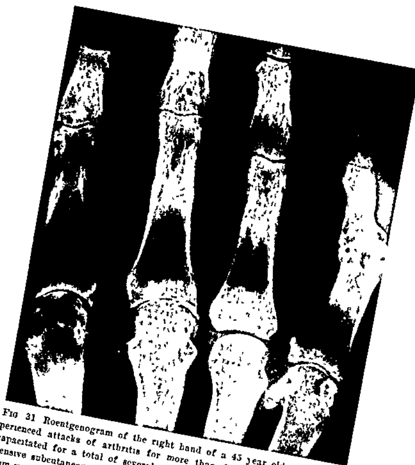


Fig 31 Roentgenogram of the right hand of a 45 year old male who had experienced attacks of arthritis for more than fifteen years He had been ncapacitated for a total of several months On physical examination he had xtensive subcutaneous urate deposits The concentration of uric acid in the erum was as high as 12 2 mg /100 ml Multiple cystic areas, narrowing of the etacarpal phalangeal joints and soft tissue changes are present



FIG. 32 Roentgenogram of the hand illustrated in FIGURE 31 after a lapse of four years There is evidence of progression of the tophaceous deposits in the metacarpal-phalangeal area of the index finger as well as evidence of healing in the little finger. The patient had received colchicine daily and Benemid irregularly.

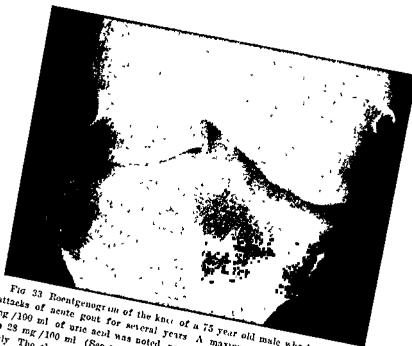


Fig 33 Roentgenogram of the knee of a 75 year old male who had suffered attacks of acute gout for several years A maximum concentration of 10 1 mg /100 ml of uric acid was noted, as well as a blood urea nitrogen as high as 28 mg /100 ml (See Fig 39) The patient was placed on daily colchicine only The changes in the medial condyle of the femur are characteristic of osteochondritis dessicans This finding is believed to be unrelated to gouty arthritis X ray film of the opposite knee was negative



FIG 34. Roentgenogram of the toe of a 38 year old male who suffered from acute attacks of gout for one year only. The father also suffered from gout. The maximum concentration of uric acid in the serum was 8 0 mg./100 ml. Accessory bones at the base of both distal phalanges of the great toes on the medial aspects are present These represent congenital variations.



FIG 35. Roentgenogram of the right foot of a 48 year old male who had suffered from gout for fifteen years The mother had gouty arthritis The patient had a congenital deformity of the left foot The metatarsal phalangeal joints of both great toes were the site of acute episodes on several occasions Clinically, there was no difference in incidence of acute bouts between the left and right foot The patient was placed on the colchicine Benemid regimen in 1950 and has not lost any time from work in the interim There are minimal changes only in the bony structures



FIG. 36 Roentgenogram of the left foot of the patient illustrated in FIGURE 35 The impaired bone development is apparent

Clinical Description

SINCE AN ACUTE ATTACK of arthritis of one or more of the joints of the extremities is the first conventional sign of articular gout, the diagnosis usually is not suspected until after this event. Nor should a diagnosis of gout be made until after the first attack of joint distress. Symptoms or findings in isolated instances, however, may precede the characteristic articular symptoms, and if identified, should be interpreted as portentous. Albuminuria, elevation of blood pressure, and the passage of a renal stone, respectively, have been noted before the initial articular episode. The incidence of each of these items after the onset of joint symptoms is well documented. It is not surprising that they precede articular manifestations in some patients. Since the disturbance in uric acid metabolism is a chronic persistent phenomenon, it should not astonish us to observe albuminuria, hypertension and renal lithiasis before as well as after the first attack of acute gout. The articular findings are fortuitous to the metabolic disturbance as noted on the section on *Intermediary Metabolism*. The presence of subcutaneous tophi before the initial attack is an exceptional observation but theoretically is possible also. This phenomenon, reported in exceptional instances by others, has not come under our observation. According to the current theory of pathogenesis of symptoms microscopic deposits of uric acid precede the initial articular attack. Why then should not macroscopic deposits be observed from time to time before the first attack? This introduction to the section on clinical findings is not intended to detract from the usual experience of the gouty patient, i.e., an acute attack of joint distress in an otherwise healthy adult male is the first indication of the metabolic dyscrasia.

Acute Attack

The typical onset of acute gout is sudden and may appear at any time during the 24 hours of the day during any day of the year. The metatarsal-phalangeal joint of the great toe usually is affected but other peripheral joints of the upper or lower extremities may be involved. The description of the acute attack by Sydenham,[219] who wrote from personal experience, begins as follows: "The Patient

goes to bed, and falls asleep in good health but about two hours after Midnight, he is awakened by a Pain, which usually affects the great Toe" As the pain becomes progressively more excruciating in a relatively short period of time, agony may be incapacitating It has been described as similar to the dislocation of a bone, the gnawing of an affected joint by an angry dog, the instillation of *molten lead into the joint or the compression of the member in a* carpenter's vise

Another classic description is that of Sir T. Clifford Albutt,[1] published in 1920.

"He becomes pettish, snappish, gloomy, he sleeps ill or too heavily, is restless or torpid, and dreams uneasily or in nightmares His head aches, with a dull heavy ache, or as a migraine An early sign is an irregularity of the bowels, the motions may be constipated or irregularly loosish, sticky, lumpy, and more offensive, and in the motions mucus may be plainly visible The belly is tumid and flatulent, and the regions of epigastrium and liver become tender, and even painful to pressure; probably a referred pain from a stretched hepatic capsule . . . The stomach is windy, the appetite falls off, and eructations, acrid or carrying savours of *former meals, are troublesome* The whole venous pressure seems to rise, so that gouty persons are liable to piles. Streaks of inflammation may be seen along the lymphatic vessels The tongue is coated, in a few cases red and stripped, but usually white upon a red ground, or carpeted with a thicker brownish fur. The patient grinds his teeth, partly because his mouth is sour, partly because there is a deeper uneasiness, as it were in their roots; a slightly alveolar periostitis has been supposed Hawking, up to vomiting, especially of a morning, may be frequent . . Disorders of the heart's function often take a large part in these phases; palpitation, intermittences, throbs, flutters Concerning the urine, we are wont to say that it is scanty and lateritious, thick with red or purplish urates"

The pain of acute gout is caused in part by an effusion into the joint cavity as well as by edema of the surrounding soft tissues The synovial capsule, somewhat inelastic, is sensitive to pressure and manifests maximal tenderness usually on the lateral aspect of an involved joint. This phenomenon may be demonstrated particularly upon examination of the proximal joint of the great toe if this member is afflicted One or more joints may be involved simultaneously during an acute bout, or several joints may be involved successively, similarly to migratory polyarthritis of acute rheumatic fever An acute gouty joint also mimics a septic process with the

cardinal signs of inflammation Garrod,[89] indeed, held that "If a medical man, by chance entirely ignorant of the nature of gout, were to see a toe affected by this disease in its full intensity, swollen, hot, red and tender, he would probably think that the affection must of necessity terminate in suppuration, yet I believe that this never happens as a result of simple gouty inflammation" The inflammation extends beyond the joint at times, with involvement of the lymphatics similar to a cellulitis Two points of differentiation should be noted which may warn the surgeon against incision and drainage for suspected infection The skin is tense and shiny in a gouty joint, and the color tends to be a cyanotic purple rather than a fiery red This is not an invariable experience, however, and at times the acute gouty joint may be indistinguishable on inspection from what would otherwise be a purulent process The coexistence of joint sepsis and acute gouty arthritis has been observed only once in our experience This episode occurred 20 years ago Correct differentiation between a septic and a gouty joint is not altogether an academic problem If sepsis is presumed, rather than gout, antibiotics might be recommended in treatment It will be noted in the section on *Precipitating Factors* that penicillin is such an offender, it may aggravate acute articular gout without in any way mitigating acute symptoms

Acute attacks of gout tend to involve articular structures only, although nonarticular tissue may be affected independently of a neighboring joint A subcutaneous tophus, a bursa or a tendon infiltrated with urate, may be acutely involved and extremely painful The systemic reaction to the acute process may be indistinguishable from that which accompanies acute sepsis Fever, chills, malaise, anorexia, headache and tachycardia may be formidable in addition to the local area of affliction A spiking fever with temperatures as high as 104°F, is not unusual in a severe articular episode and may confuse the physician as well as debilitate the patient Figure 37 portrays the experimental observations on one patient during an acute bout Another example is the patient with chronic tophaceous gout who was admitted to the hospital with acute involvement of several joints A highly competent clinician responsible for his medical case, but one with very little experience with acute gout, was reasonably certain that the febrile response indicated infection

it required some persuasion to withhold antibiotics Forty-eight hours later, following a full course of colchicine, the fever had abated and the joint symptoms had cleared markedly.

The urine output may be scant, as with any acute febrile response if abundant quantities of fluids are not ingested A leukocytosis and an increase in the sedimentation rate may be observed Large joints, notably the knee, may be the site of a massive effusion

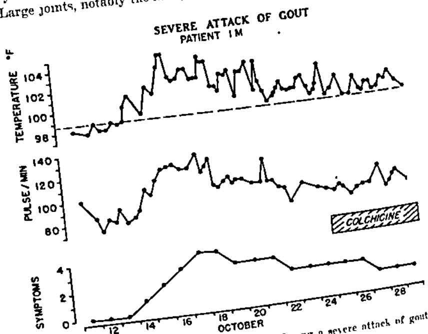


Fig 37 The pulse and temperature response during a severe attack of gout

If specific measures are not instituted, the duration of an attack is unpredictable The first attack may be of short duration and subside within a few hours as rapidly as it appeared, without the counsel of a physician, or it may persist for several days or even several weeks The unpredictability of the severity and the duration of an acute attack has proved a pitfall at times in the therapeutic evaluation of various anti-gout procedures.

A 49 year old male, A T., whose family history is positive for gout, had intermittent attacks of acute articular distress for more

in the ten-year period, the most recent attack four months prior to the hospital admission The metatarsal-phalangeal joint of the great toe has been involved during each bout The longest period of incapacity was 20 days Colchicine was prescribed for the first attack but was discarded subsequently when the diagnosis of gout was questioned

Proper management of the acute attack should lead to significant improvement and partial rehabilitation within 24 hours and essentially normal function not more than 72 hours after beginning therapy In the case of a severe attack, either untreated or inadequately treated, one or more weeks may elapse before rehabilitation appears Occasionally one encounters a patient with severe joint symptoms which persist for several weeks, either as a result of a repetitive series of single attacks or of one prolonged episode Rutledge and Bedard[206] reported a striking example of incapacity A 34 year old male was bedridden or chair-bound for more than sixteen months in the course of twelve attacks of acute gout over a period of nine years The diagnosis of gout had not been made, possibly because no tophi were demonstrated Patients with advanced gouty changes and extensive urate deposits are more prone to prolonged bouts of articular distress than those mildly afflicted This statement is particularly applicable to those patients who are not on prophylactic therapy Anti-gout agents, prophylactic and therapeutic, are important factors in preventing attacks, aborting mild ones, and markedly shortening the duration of severe ones, respectively

The subsidence of an attack is accompanied by diminution of local inflammation and regression of systemic symptoms If the acute attack has persisted for several days, desquamation of the surrounding area (PLATE X) may be noted after normal function has returned Once the acute symptoms have subsided, the sooner normal function is resumed, the better the clinical result Restoration of function sometimes is delayed unnecessarily because of the reluctance of patients to use a joint recently affected, particularly if the joint is a weight-bearing structure

The site of acute gouty arthritis is relatively constant, the metatarsal-phalangeal joint of the great toe, right or left, without discrimination, being most susceptible. Scudamore,[213] in 1823, collected a number of observations on this subject. The great toe on one foot only was involved initially in approximately 60 per cent of a total of 516 cases Both toes were involved initially in 27 cases. instep, ankle, heel, knee and hand, respectively, were affected in the remainder of the group In our series, the toes, ankles, knees, wrists, fingers and elbows have been affected in this order. The hips, spine, sacro-iliac, sternoclavicular and mandibular joints are attacked infrequently, but specific involvement in each area has been documented. Tophaceous softening of the cervical vertebrae with subluxation has been reported by Kersley and associates[136] and by Kosokoff.[140]

Premonitory symptoms were the object of considerable attention in the older literature on gout. Vasomotor instability, flatulence, constipation, epigastric distress, depression, insomnia and palpitations have reputedly preceded an acute attack Undoubtedly, persons may have a premonition of an impending attack, but some of the symptoms may be attributed to, or be associated with, precipitating factors and need not be an integral part of the incipient stages of acute gouty arthritis. If one or more of these complaints are observed repetitively as an individual variation, such a patient should be encouraged to appreciate their significance and heed the warning of an impending attack and begin specific therapy in advance of articular distress

The interval between attacks varies considerably. Several years may elapse; in unusual instances, a score of years may separate the initial attacks in the early years after onset of articular symptoms As the disease progresses, the frequency of attacks tends to be augmented in spite of the absence in many patients of clinical evidence of chronic tophaceous gout Patients who show gross deposition of urates in and about the joints of the extremities are prone to suffer greater incapacity from acute gouty arthritis per year unless prophylactic therapy is followed.

The following unsolicited letter is an illustration of the desperate plight of some individuals.

"Dear Doctor.

I sincerely hope this letter reaches you and that you can help me as I am getting to the point where it is only a question, as to whether I shall go on or not. I have a bad case of gout, so analyzed by several physicians, through x rays, blood and uric acid tests, etc etc

"I have taken pills, liquids, powders, etc, etc, until I am almost a pill I am on a very strict diet of mostly fruit and vegetables of some kind I do not eat meat, fish, or fowl, no spices, fats, or liquor I do eat a little cheese and eggs I have never eaten rich or spicy or fatty foods. I never was a drinker Once in a while a highball, but seldom I have never had a venereal disease

"I am 67 years old and in fairly good health otherwise Blood pressure is normal, no heart condition

"Just completed x rays of entire body, spine, stomach, gallbladder, etc No complications

"Have been to several doctors the past four months, and no one seems to help me I am now taking ——— tablets Was taking ——— tablets, both above by doctor's instructions Have had numerous injections of ———

"The pain in my feet and legs at times is unbearable I cannot go to work, my bills are accumulating I am worried Can you suggest something to help me? Shall I take ———? I suggested this to several well known M D 's here, however, they advised the above tablets, which do not help me at all I have used ——— ointment and ——— to relieve pain It gives me a little temporary relief "

Intercritical Period

Between the acute attacks, in patients without articular deformities, there are no subjective symptoms or objective findings Hench enjoys relating the tale of the athlete with gout in ancient times who won an Olympic marathon in the intercritical period [8] The period between attacks in some patients may be several years Patients who, in the fifth, sixth, or seventh decade of life, suffer the first attack of acute arthritis in a mild form may have no more than a few attacks during the remainder of their lives and may die of an unrelated malady A small percentage of patients with an unusually benign type of gout may appear to be completely immune to acute episodes after one or a few bouts of gouty arthritis and without continuous or prophylactic therapy This situation may be comparable to the patient seen infrequently in the diabetes clinic who is able to maintain a sugar-free urine and a normal blood sugar after dietary regulation and with conservative measures only The following example illustrates the unusually mild type of gout

H C, the manager of a trucking company, is able to hold his own with his truck drivers in minor as well as major matters His first attack of acute gouty arthritis caused him more misery than probably he had ever experienced in his life He was convinced that the Devil was beginning to balance the books prematurely His acute symptoms were relieved with colchicine, and within 48 hours all evidence of acute gout was gone Because of his obesity, it was recommended that he reduce 25 pounds in body weight. The diet allowed included proteins daily and eliminating only those items high in

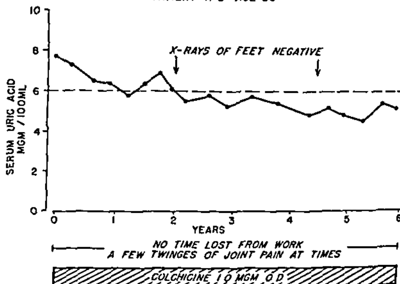


FIG 38 Experimental observations upon the concentration of serum uric acid over a span of six years The only drug prescribed was colchicine daily The return to normal in urate concentration without benefit of uricosuric drugs is unusual in our experience

purine substances, such as liver, kidneys and sweetbreads A high fluid intake, with alcohol in moderation, and two colchicine tablets a day were among the recommendations The transformation during the following year surprised his friends as well as his physician The desired excess body weight was lost, sensible rules of living were followed and an interest in civic enterprises developed Prophylactic colchicine has been taken regularly for eight years, and there has been no recurrence of acute gout The concentration of uric acid in the serum has fallen steadily (FIG 38) This trend of the uric acid in the serum without the use of uricosuric agents in my experience is the exception

Chronic Gout

Chronic deforming changes are observed in only a small number of the total gout population Nor does the presence of subcutaneous tophi mean persistent symptoms of chronic joint involvement Effective prophylactic medication in a severely afflicted patient leaves the irreparable damage to joint function and the mechanical interference from urate deposits as the only incapacity In the case of the only two patients in our experience with gout to become bedridden from gouty arthritis, the first patient had the most extensive urate deposits that we have seen (PLATE IX) He died at the age of 35, having been bedridden for several years Extensive surgery had been necessary from time to time over a period of fifteen years The last major operation was amputation of the left leg below the knee The second patient had ankylosis of several large joints [156]

The joints that are the site of acute arthritis likewise are the site of chronic deforming changes The feet (PLATE XI), ankles, knees and hands reveal evidence on physical or x-ray examination of chronic deforming changes The elbows (PLATE XII), shoulders, hips, sacroiliac joints and spine may be involved with or without demonstrable subcutaneous tophi in the periarticular structures Large subcutaneous tophi may break down and discharge urate sludge Tophi of the feet, hands, elbows and buttocks have formed sinuses in the patients in our series Tophi of the nares have been reported from two clinics [66, 174]

Precipitating Agents

A NUMBER OF AGENTS OR FACTORS, either individually or in combination, may be responsible for inciting acute attacks Recognition of the several items is of practical significance and should be appreciated by patient and physician Among these items, overindulgence in rich food, alcohol and sex occupy prominent positions in the older literature "A Greek anthologist sings, that of the limb-loosing Bacchus and the limb-loosing Aphrodite is born the daughter, limb-loosing Podagra "[3] In the opinion of this writer, no satisfactory evidence in support of the first two categories as inti-

mately responsible for an acute attack has been adduced While the insult to the body is believed to be general, yet any insult to the body, general or local, conceivably may be an inciting agent. The matter of sex is supported by even less statistical evidence A limited number of patients with gout seen in this clinic have volunteered the admission of a diminution in libido prematurely. It is probably difficult to evaluate "prematurely" in any case, but especially so in a chronic malady such as gout. On the other hand, information tendered by at least two patients leads us to suspect the fallacy in this area. One male in his late 70's and another in his early 80's, both with gout, have volunteered without boasting, persistence of libido and retention of sexual capacity.

The hereditary metabolic nature of this malady would seem to make gout immune to incidental items such as food and drink The presumption that particular foods, except those of high purine content, are harmful to gouty patients is not merely an empiric observation, it is a prejudice Even foods high in nitrogen and purine substances sometimes fail to incite an acute attack and are not particularly reliable as a provocative agent in the diagnosis of the malady There are several agents that have in selected instances a closer relationship to acute gouty arthritis than do food and drink. These include drugs, trauma, acute infections, blood loss, prolonged bedrest[72] and surgical operations[115]

W C, a 57 year old white male, first seen in 1952, was suffering from acute articular gout of the metatarsal phalangeal joints in both the right and the left foot The distress appeared several days following surgery for repair of an inguinal hernia. The family history was negative for gout His own history revealed a functionless kidney from tuberculosis The urine showed a 3 + albuminuria The P S P excretion was 55 per cent in two hours. The maximum specific gravity of the urine was 1 018 The blood pressure was normal. Since this was the first attack of gout, the patient was not placed on Benemid. Colchicine, 0 5 mg daily, was recommended The serum levels are shown in FIGURE 6 W C has not had any trouble in the intervening four years.

Sydenham urged patients to "keep the mind quiet" in order to avoid acute gout There are a number of examples among our patients of emotional trauma provoking an acute attack, such as the following record.

R D, a white male, was seen first in 1949 at the age of 33. As a tavern keeper he probably eats and drinks more than is good for him. He gave a history of having suffered from intermittent attacks of acute gout since the age of 25. There was no past history of hypertension, renal stones or albuminuria. In spite of taking colchicine and Benemid rather regularly, he has responded poorly to the regimen, possibly not so severe as before beginning the regimen, but nevertheless, incapacitated for several days each year. Some of the greatest difficulty occurred during the year that he was under severe emotional tension associated with the granting of a divorce. When the legal matters were settled, the acute attacks diminished significantly. During the following two years, the days of incapacity have been reduced markedly.

There are several drugs that should be given to gouty patients only after due deliberation and consideration of the need for them. Parenteral penicillin should be prescribed to gouty patients only if there are sound clinical indications, since penicillin administration may be followed by an acute gouty episode. Thiamine chloride, vitamin B_{12}, insulin and ergotamine tartrate have been implicated as inciting agents. Price [193] reported five instances of acute gout following a diuresis induced in edematous patients by a mercurial diuretic. Articular symptoms appeared from seven to nine days after administration of the diuretic. Since each patient in this series died within two months of this episode, it was interpreted as one of grave prognostic significance. We have observed acute gout following an induced diuresis but no other untoward effects. One patient in our series, J B, has been in chronic cardiac failure for several years. Mercurial diuretics have been administered as frequently as twice a week, meanwhile he takes colchicine regularly. His gout is mild and he has not had an acute bout of gout for more than three years. Undoubtedly, the list of inciting drugs might be lengthened considerably. Since the pharmacologic action of these substances covers a wide range of function, the mechanism of the side effect is thought to be general rather than specific.

Direct trauma offers a readily acceptable explanation. A joint, already the victim of urate deposition, may be incited to inflammation by a blow. In the earlier years of the natural history of this malady, the diagnosis of gout may be overlooked following direct trauma.

Mr A T., a 44 year old male, suffered a minor injury to his ankle while in college. The ankle was strapped and recovery was slow It was noted at that time that the morbidity seemed inconsistent with the mild trauma sustained. Five years later, the left great toe became inflamed, with acute symptoms persisting for several days When, three years later, the opposite toe became affected in a similar manner, the diagnosis of gout was then suspected The concentration of uric acid in the serum was 7 5 mg /100 ml In spite of the difficulty in fixing the responsibility for the alleged "sprained ankle," in all reason we may conclude the case represented an acute attack of gout following minor physical trauma

S G, a white male, was seen first in 1949 at the age of 34. On the occasion of the first attack of articular distress three years before, a diagnosis of gout was made The concentration of uric acid in the serum was 11 mg /100 ml The patient was placed on colchicine, 1 0 mg daily, and responded well While at work in 1952, he stepped on a nail and received tetanus antitoxin prophylactically After several days the left ankle became red and swollen, and, in succession, likewise the left knee, the shoulder and left wrist For a period of seven weeks there was intermittent joint distress attributed to "infectious arthritis" by his family physician, in spite of the previous diagnosis of gout Eventually, in response to the insistence of the patient upon the gouty origin of the symptoms, a full course of colchicine was prescribed His rapid response won a discharge in three days. He continued, however, to take colchicine daily, and remained symptom free until the following year, when he suffered an injury to his foot. For the next five weeks, under his doctor's care including a period of hospitalization, numerous agents were tried, but the acute arthritis in the hands and feet persisted The patient finally insisted upon a full course of colchicine Once more the response was satisfactory and he was discharged symptom free in five days In each instance it should be noted that the patient was under the care of his family physician, who was unwilling to accept the diagnosis of acute gouty arthritis precipitated by an external agent The excellent response to colchicine is convincing evidence that each episode represented acute gout following an insult

Ill-fitting shoes and gloves may cause sufficient irritation to precipitate an acute attack Local x-ray therapy may also be responsible Acute infections are frequent associates of gout An acute pharyngitis, sinusitis or furunculosis may be complicated a few days later by acute articular distress Major infections may also be offenders Acute gout has been associated with convalescence from an acute myocardial infarction [8] Inclement weather, with or without direct exposure of the body to the elements, may be followed by acute gout The association of a decrease in barometric pressure

with articular symptoms is believed to be another example of a nonspecific insult to a susceptible subject When the causal relationship is sufficiently precise, as is the case in some patients, prophylactic therapy may be considered [216]

Complications

KIDNEY IMPAIRMENT, with varying severity of hypertension and arteriosclerosis, is the only critical complication of gout In spite of the frequency of this complication, in only a small percentage of cases does it result in uremia and premature death The oft-quoted observation of Gudzent [101] that only four of a total of 77 autopsied cases of gout showed no evidence of kidney disease needs interpretation before drawing sweeping conclusions The detection of structural changes in the kidney does not imply serious dysfunction of this organ In fact, there are several patients under our observation who have laboratory evidence of well-developed renal disturbance without significant reduction in longevity (FIG 39) Among all of the patients with gout in this clinic, almost 50 per cent show some evidence of renal dysfunction However, only 6 per cent show a persistent increase in the concentration of blood urea nitrogen (FIG 40), and only three patients have died during the past decade prematurely because of uremia Several deaths, to be sure, have occurred from causes not related directly to severe renal insufficiency

The detection of kidney involvement in the initial stages of the natural history of gout depends upon routine laboratory findings, i e, albuminuria, cells or casts in the sediment, impaired concentrating ability, increased concentration of urea in the blood, and abnormal intravenous pyelography, respectively The first four laboratory procedures have been performed routinely in each patient with gout seen in this clinic; the fifth procedure has been performed if it seemed indicated The various terms applied to the kidney involvement in gout and mentioned in the discussion of *Pathology* indicate the lack of definitive characteristics, clinical as well as pathologic A slight trace of albumin and a few formed

elements in the centrifuged sediment may precede by several years the initial articular symptoms, the passage of a renal stone or urate gravel. Impaired excretion of phenolsulfonphthalein dye, inability to concentrate solids and poor function, as noted during intravenous pyelography, appear in the course of regression of renal per-

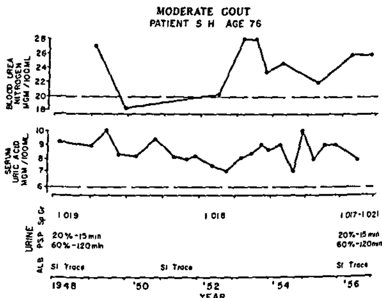


FIG 39 Experimental observations on a 75 year old carpenter who had suffered acute attacks of gout for a number of years. Colchicine was the only drug prescribed for an eight year period. During this time the concentration of blood urea nitrogen was above normal in all except one determination and the urine, repeatedly, showed a trace of albumin The P.S P. excretion in the urine was normal and the specific gravity of the urine was essentially normal.

formance Persistent nitrogen retention, when observed, is a late manifestation The interval between the appearance of albuminuria and the development of nitrogen retention may be several decades

The protracted course of renal dysfunction in gouty patients with demonstrable renal disease is characteristic. A diagnosis of chronic nephritis might be assumed if proper emphasis were not given to the history or present findings of joint symptoms Nor is a diagnosis of chronic nephritis definitely justified in spite of the

several suggestive features, although I appreciate the lack of entirely satisfactory evidence in support of this statement The reason for this assumption, nevertheless, rests upon the chronicity of the kidney changes as well as upon the failure to observe in patients with gout the clinical counterpart of subacute nephritis, a phenomenon which has a relatively high incidence in patients with

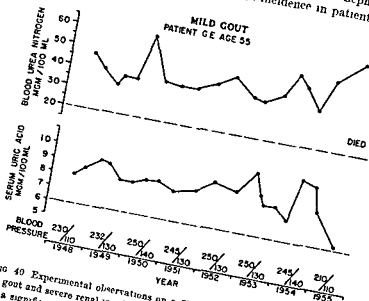


FIG 40 Experimental observations on a 55 year old male who suffered from mild gout and severe renal insufficiency He was followed for almost seven years with a significant elevation of blood urea nitrogen and a blood pressure in the malignant hypertensive range The patient died in uremia.

typical chronic glomerulonephritis Furthermore, the pathologic findings in kidneys of patients with gout do not correspond, in many reported cases, to those of chronic glomerulonephritis

Albuminuria, usually the first evidence of renal disturbance, was noted in 21 per cent of a series of cases reported by Brockner-Mortensen [88] Precipitation of urates in the tubules seems a reasonable explanation for this disturbance Blockage of the tubular lumen, degeneration of the epithelium, atrophy of the nephron and destruc-

tion of the glomerulus follow. The small vessels in the parenchyma share ultimately in the degenerative process. Regression in glomerular filtration rate accompanies depression in renal blood flow. The predominant arteriolar constriction such as is observed in patients with essential hypertension is lacking.[56]

A kidney repeatedly subjected to insult from the precipitated crystalloids is believed to be more susceptible to secondary pathologic processes. Thus, a pathogenic organism in the genito-urinary tract may find a suitable environment for growth and development of pyelonephritis, which, in turn, predisposes to calcium stone formation, especially by urea-splitting bacteria. Hence, calcium stones, as well as urate stones, may be formed in gouty patients.

Renal stones constitute an interesting as well as an important clinical complication in gout (PLATE XIII). At the time the illustrious sufferer from gout, Benjamin Franklin, was troubled with urate gravel and bladder stones,[57] his esteemed friend and fellow scientist, the famous Dr. William Heberden of London, whose name is attached to the exostoses in osteoarthritis, was consulted regarding Franklin's gout. His reply in a letter prepared in 1785 regarding surgery for the bladder stone was in the negative.

Gairdner [85] reports one gouty patient with stone trouble as follows:

"The Patient is now in his 79th year. When a young Man he was sometimes troubled with gravelly Complaints. But they wore off without the use of any medicine and he remained more than Fifty Years free from them.

"In the Autumn of 1872, he had a severe Attack accompanied with what he thought to be Gouty Pain in the Hip, and down the Thigh of the left Side. . . . He daily voided Gravel Stones the Size of small Pease, took now and then some Decoctions of Herbs & Roots . . .

"At length the painful Part of the Disorder left him, and no more large Gravel offer'd, but observing Sand constantly in his Urine . . ."

Wells,[285] a century ago, labeled the urate concretions *pisiform deposits* and noted that ". . . it is really remarkable what an enormous number of these minute calculi are frequently passed. I have met with cases in which upwards of 200, the size and color of mustard seeds, have been passed in two days."

Kittredge and Downs [135] analyzed the records of 324 male patients with gout admitted to the Ochsner Clinic during the nine-

year period ending in 1950 Fourteen per cent had had stones that were recovered or were demonstrated roentgenographically prior to admission An additional 3 per cent gave a typical history of renal colic although stones were neither recovered nor demonstrated roentgenographically The incidence, therefore, of renal stones in this series is approximately 17 per cent, a value precisely the same as reported by Brockner-Mortensen in 100 patients with gout [illegible] The incidence in our clinic is 16 per cent Calculi from fourteen cases of Kittredge and Downs were available for analysis, 64 per cent of the stones were composed of pure uric acid, two-thirds of these were not visible radiographically prior to the passage In addition to urates, the remaining 36 per cent of the stones contained quantities of other elements Interestingly enough, a stone may have a nucleus of uric acid and yet be composed principally of calcium phosphate during formation Most important, then, is the identification of the nucleus if uric acid is suspected as being responsible Of the 45 patients with proved stones in the series, 53 per cent were multiple and 31 per cent were bilateral Ninety three per cent were of renal origin, and in three patients the stones were removed from the bladder Sherwood [219] in a study of the incidence of articular gout in 50 patients suffering from urate lithiasis, found the incidence to be 10 per cent In a comprehensive study by Boyce [34] of urinary calculi, 22 per cent of the patients who passed pure uric acid stones had hyperuricemia The incidence of gout was the same as reported by Sherwood, i e , 10 per cent In a somewhat different approach to the stone problem by Hauge and Harvald,[112] a history of renal stones in 20 of 261 relatives of gouty patients was obtained, a result similar to the incidence of hyperuricemia in this number No mention was made of the incidence of concomitant stone and hyperuricemia

Prien and Frondel [197] have presented an excellent discussion of urate stones I quote

"Uric acid occurs most often in calculi in a pure state Apatite and calcium oxalate monohydrate are its most common associates in calculi of mixed composition It may occur as the nucleus in calculi composed of calcium oxalate monohydrate or of apatite The latter substance may also be found in the interstices of coarsely porous uric acid calculi Calcium oxalate monohydrate has also been found as the nucleus of a uric acid stone.

"Uric acid calculi have a dense, fine-grained structure and are relativel heavy. An oblate or flattened pebble like shape with a smooth but not polished surface is rather typical. Warty surfaces are sometimes observed Cross sections of the stones usually show a concentric lamination of variable coarse ness with radial striation Alternating light and dark laminations are of identical composition, the dark layers probably being due to pigmentation Some calculi have a granular appearance without evidence of lamination The nucleus is commonly composed of unoriented uric acid crystals The color is usually some shade of brown with which red or orange may be mixed

". . . A number of different urates, including both the acid and normal salts of NH_4, Na, K and Mg, have been described in urate calculi . . . it seems quite obvious that urates occur far less commonly in calculi than would appear from the results of chemical analysis . . .

"Sodium acid urate was found but once and in microscopic amounts in our series of approximately 700 urinary calculi"

There is no predictable pattern for the incidence of symptoms from stones in gouty patients

W S, a 58 year old white male, has evinced symptoms of renal lithiasis on many occasions His gouty arthritis is classified as severe with subcutane ous tophi There is a strong family history for this malady. The first evi dence of a renal stone, at the age of 26, preceded the initial acute articular episode by ten years During the subsequent 25 years it has been estimated that he passed more than twenty stones. On two occasions it was necessary to remove them surgically The second operation for lithiasis was in 1944 Whenever the stones have been analyzed, a high urate content has been reported For the past six years, on the colchicine Benemid regimen, no large stones have been passed, and W S has suffered no incapacity from acute gouty arthritis This is the most persistent stone former in our series The stones vary in color but usually are brownish or brick red

Boyce has attributed the brick-red color to the organic matrix of mucoproteins, an organic matrix so widely distributed throughout the stone as to account for the concentric laminations.

A similar, but less severe case, follows:

C K was a 49 year old white male with mild gout and with one brother also so afflicted After his first attack in his 30th year he passed five stones in the next ten years The first attack of gout developed five years after the initial bout of renal colic At present, C K. has been on the colchicine Benemid regimen for six years (1950–56) with no days of incapacity from gouty arthritis or renal calculi No stones were passed from 1946 until 1954. Four small stones were passed in 1955 and 1956.

While this is the record among our patients, the incidence per decade on Benemid is not unlike the incidence in the earlier years of symptoms.

Although calcium stones are the exception in patients with gout, this possibility should not be overlooked. One patient, with a four-year history of gout and a positive family history, passed a urate stone shortly after the initial attack of gout. X-ray films taken recently show three shadows within the left kidney that are highly suggestive of calcium containing calculi. There is one reference in the literature to a staghorn calcium calculus in a patient with gout,[74] as well as to a staghorn urate calculus.[181]

At present the effect of modern treatment upon the progression of the renal changes in gout cannot be determined. It is our impression that patients on a daily regimen of colchicine and Benemid show no evidence of progression of renal dysfunction. Nor do we have a patient on the colchicine-Benemid regimen who has progressed from insignificant to critical renal dysfunction under observation. A much longer period of study will be needed, however, before definitive conclusions in this regard are forthcoming. Meanwhile, we are hopeful that the renal lesions may be partially reversible. If mobilization of urate deposits in the kidney occurs as it does in other structures in the body under the action of a powerful uricosuric agent, restoration or regeneration of functioning cells of the kidney should occur. The degree of restoration will be dependent largely upon the extent of renal damage at the time treatment is begun.

Hypertension and *arteriosclerosis*, frequently seen in gouty patients, are considered by some observers to be integral aspects of gout. Interpretation of these morbid processes is not entirely satisfactory, however. The hypertension follows the pattern of a benign, rather than of a malignant, type. An attractive explanation is the development of hypertension on the basis of renal damage as described above. Also, there is a relatively good correlation clinically between hypertension and mild renal dysfunction. Beyond this statement, one may merely speculate. We have observed only one patient with gout during the past ten years who has satisfied the criteria for the diagnosis of progressive malignant hypertension.

The incidence of coronary sclerosis in patients with gout has been a debatable issue for many years.[8] I do not believe that patients with gout are more prone to the development of coronary artery disease than nongouty individuals. In the current series there have

been no patients succumbing "prematurely" to coronary heart disease. By prematurely, I mean prior to the age of 50 The youngest patient with gout in the current series who has died of coronary heart disease was 58 at death. The next youngest was 72. I take no stock in the "coronary artery diathesis" as an occult manifestation of gout

Large vessel sclerosis appears to develop prematurely in some gouty patients (FIG 30) Until recently, we had not seen a patient with gout develop an arteriosclerotic aneurysm of the abdominal aorta, although examples had been reported. Within a period of a few weeks one patient died of a dissecting aneurysm at the Buffal General Hospital, and another patient was reported to us from the Barnes Hospital in St Louis A considerable period of time may elapse before this coincidence is repeated

Deposits of uric acid in the endocardium and in the walls of great vessels have been reported in a small number of cases Traut,[253] describing the necropsy observations in two cases, mentioned clinical evidence of extensive chronic tophaceous gout in each Cleft-like spaces were noted between the vascular channels in an organized thrombus of the mesenteric artery of one of these patients, a 50 year old male whose blood pressure was as high 240/140, and with a plasma uric acid value as high 13 1 mg. Crysta were also found in hyalinized connective tissue of the thickene intima in a coronary artery Even without chemical identification, there was adequate evidence of the deposition of urates in the walls of the vessels The second patient, after a long history of gouty arthritis, died of an osteosarcoma of the spine associated with Paget's disease Death was due to pyelonephritis. The undersurfaces of the mitral leaflets showed deposits of chalky urates extending down over the parietal endocardium. Bunim and McEwen [46] also have described a tophus embedded in one of the leaflets of the mitral valve

Thrombophlebitis is another unusual complication of gout Paget [184] cited five instances of gout and thrombophlebitis in 1866 Garrod [90] discussed thirteen such cases Three developed phlebitis during an acute gouty episode Recently, Diamond [64] has brought this subject up-to-date A total of 287 cases of gout were reviewed;

thrombophlebitis was observed in ten There were examples of phlebitis associated with the acute attack of gouty arthritis, in other patients, there was no close chronologic relationship The first patient is particularly interesting, since it is logical to assume the presence of phlebitis over a period of ten years prior to the first attack of acute gout The clinical diagnosis of acute superficial thrombophlebitis was made on several occasions because of the cardinal signs of inflammation about the ankle On the one hand, possibly acute gout was present at the time of the acute phlebitis or on the other hand, in the absence of acute joint symptoms, a logical assumption from the record, we have another example of one of the associated phenomena in gout actually preceding by a decade the onset of acute articular symptoms Three of the ten cases with gout and thrombophlebitis were females The arm, thigh and lower leg were involved, respectively

Our clinical experience has been enriched recently by two patients with phlebitis F D'A , a 57 year old male with a positive family history for gout was treated for acute phlebitis of the lower leg during one of his earlier articular episodes In the absence of a diagnosis of gout at that time, emphasis was centered upon the clinical findings of thrombophlebitis Another patient T D a 40 year old male entered the hospital with acute gouty arthritis of the right knee and a large synovial effusion Five days after the onset of articular symptoms, phlebitis of the medial aspect of the lower leg was observed This subsided within 48 hours without any specific therapy except the anti-gout agents prescribed for the articular symptoms

Ocular findings have been ignored in previous discussions of gout by the author because of meager clinical experience as well as skepticism regarding a direct association between morbid processes in the eye and a disturbance of uric acid metabolism The only reference to the eye concerned the monograph by Weve [266] published in 1924 The subject has been reviewed by McWilliams,[170] and it seems inappropriate to continue to ignore this vital organ Jonathan Hutchinson [126] is accredited with the term "hot eye" of gout, the conjunctiva is injected, leading to a hot and prickly sensation in the lids Episodes are transient and followed by iridocyclitis Hutchin-

son also described a destructive iridocyclitis in offspring of gouty parents. Iritis, corneal ulcer, scleritis and episcleritis have been observed in patients with gout. Uric acid crystals may be found in either of the latter two disturbances. Wood[274] observed thickening of the sclera and infiltration with lymphocytes and plasma cells. On the posterior surface of one eye of a patient who suffered from recurrent attacks of tenonitis, patches of urate crystals were identified. McWilliams[170] reported one instance of a tophus on either side of the cornea in a patient with subcutaneous tophi on the extremities. The ocular tophi were fixed to the episcleral tissue. Funduscopic examination was negative.

Associated Diseases

SEVERAL DISEASE ENTITIES have been associated with gout in the natural history of the malady. Contemporary literature on this subject, except for the blood dyscrasias, is scant in comparison with the reports in the nineteenth century. The associated disturbances noted have included lead intoxication,[89] diabetes mellitus,[94] obesity,[70] hypercholesterolemia,[2] essential lipemia,[83] polycythemia vera,[252] leukemia, myelofibrosis[1] and multiple myeloma.[9]

Exposure to lead as a causative agent in the production of gout was a popular assumption in England and Germany a centur ago[89, 158] Recently two examples of "lead gout" have been reportec in France[264] We have seen a few cases of gout with a history of lead intoxication and gouty arthritis Although control of the lead problem in industry is relatively satisfactory, the widespread use of this heavy metal and the low incidence of gout among exposed workers suggests no causal relationship Among the industries in the Buffalo area there is considerable exposure to lead However, none of the three patients in our gout series who have had varying degrees of exposure show clinical evidence of lead intoxication The response to anti-gout drugs in each patient has been as predicted in spite of repeated exposure to the heavy metal. The three patients noted in the following paragraph developed initial joint symptoms in the same lead battery manufacturing plant.

F.D., a 50 year old foreman in the plant, with a ten year history of gout has shown no symptoms or laboratory evidence of lead intoxication. When seen first in 1947, he stated that he was forced to accept from one to two weeks of incapacity each year because of acute gouty arthritis. Colchicine, 0.5 mg b.i.d., was started at that time. He continued to experience several *mild attacks each year, but none so severe as to cause loss of time from* work. Early in 1954, Benemid, 0.5 Gm t.i.d., was added to colchicine. The following year the intake of Benemid was decreased to 0.5 Gm b.i.d. During the three year period on this regimen only one mild attack has occurred, again not severe enough to keep him from work. Several years after F.D.'s first attack, one brother with no history of lead exposure developed gouty arthritis. Two other workers in the same plant suffered from gout, but in none of these three instances was lead intoxication under suspicion or judged to be an etiologic factor in the production of gouty arthritis.

The coincidence of diabetes mellitus and gout is low.[128] There are two patients with gout in the current series who have mild diabetes mellitus controlled by diet. These examples are similar to the case of the patient described by Engelhardt and Wagner,[70] who did not require insulin for regulation but showed a blood sugar as high as 280 mg./100 ml. during a glucose tolerance test.

Although the patients with gout appear to be somewhat prone to obesity, no good statistical data support this deduction. With but a few exceptions, the patients in our series are not overweight. The reasons for cautioning against obesity are largely general, although obesity puts an added load upon weight-bearing joints.

Adlersberg[2] has reported a series of 27 patients in hypercholesterolemic families. One third had hyperuricemia, one third had borderline values for serum urate (between 5 and 6 mg./100 ml.); the values in the others were less than 5 mg. Several members of the family had characteristic manifestations of gouty arthritis.

Metabolic maladies of unknown etiology found coexisting with gout are Paget's disease, osteogenesis imperfecta, Morgagni-Stewart-Morel syndrome,[75] and pseudo-pseudohypoparathyroidism.[260] Garrod[90] observed three patients with Paget's disease and gout. After the eponymic term of the former malady had been introduced, Paget[183] commented upon the coincidence. Serre and Mirowze[216] reported four instances of the coexisting maladies. A reasonable explanation is the incidence of the respective diseases in mature males. There is no recognized chemical disturbance common to both maladies to account for the articular changes. Allen and associates[4]

studied three cases of osteogenesis imperfecta tarda Two patients were father and son A serum urate of 14 4 mg. was observed at one time as well as a poor response to anti-gout agents

The blood dyscrasias occupy the significant position as diseases associated with gout Polycythemia vera, leukemia, myelofibrosis, and multiple myeloma as well as lymphoblastoma, pernicious anemia, hemolytic anemia and Cooley's anemia merit consideration When articular gout appears in association with one of the bl disorders, it has been attributed to acceleration in the degradat of nucleic acids, an increase in production of precursors of uric ac and an increase in concentration of serum uric acid With a hig level of uric acid in the blood, the possibility of precipitation in th joints is real, and if the elevation is persistent for a long period, precisely the same effect upon the joints as appears in hereditary gout may be anticipated Serum urate values as high as 36 and 38 mg./100 ml have been observed[263] Such values appear out of proportion to the severity of articular distress.

The incidence of polycythemia and gout has been reported to be as high as 5 per cent. Tinney[252] reviewed 168 cases of polycythemia vera and identified eight cases of gout. Although the white count was elevated in several, no mention of "leukemia" was made Two patients in the group had renal colic; typical x-ray changes of gout in the great toe were observed in one patient. Videbaek[255] discovered eleven cases of gouty arthritis in a survey of 125 cases of polycythemia In eight instances, symptoms of gout appeared from two months to three years before polycythemia was detected When clinical symptoms of gout appear during or after the initial symptoms of polycythemia, this may well be called secondary gout[103] On the other hand, when symptoms of arthritis appear a number of years before clinical evidence of polycythemia, there is some likelihood of the separate entity of the two diseases. Several years ago the oxygen capacity was determined in twenty patients with gout in our series in order to evaluate the incidenc of latent polycythemia in gout patients References in the literatur suggested that the hemoglobin concentration in gouty patients might be somewhat higher than for nongouty controls Our experimental observations did not support this presumption

Hickling[117] presented the data on nine patients with gout

who had splenomegaly and immature white cells in the circulating blood A diagnosis of polycythemia was made in five Four of the nine suffered from gouty arthritis before any symptoms of the blood disorder appeared Attacks of gout began one, three, eight and forty-one years, respectively, before the splenomegaly was discovered In the other patients attacks of gout appeared one, two, four, five and eleven years, respectively, after splenomegaly was discovered In three of the nine patients, chronic gouty arthritis was the chief cause of disability near the end of their lives X-ray therapy to the enlarged spleen produced diminishingly favorable effects in subsequent courses, and in one patient, precipitated an attack of gout The bone marrow was hyperplastic in eight of the nine patients The relatively high sex ratio of females vs males in this group is noteworthy

In spite of the possible occurrence of an elevated white blood cell count in polycythemia vera, no evidence of leukemia in addition appeared in any of the cases described above Although leukemia, with an increased nucleic acid turnover, would seem to offer a greater opportunity for the development of gout, this outcome has not been substantiated in our clinical experience Increased metabolism of any one of the three major bone marrow elements, erythroblasts, leukoblasts or megakaryocytes, should lead to an increased concentration of circulating uric acid with the threat of deposition in joints and kidneys Nevertheless, instances of the garden variety of leukemia and gout are sparse in the medical literature [81, 212, 257] The inaugural dissertation by Gluckman [92] in 1910 reviewed six cases from the literature with lymphatic cell type in each case The white count was as high as 104,000 in one instance, and, in another, 202,000 Schultz [212] described the clinical course of a 21 year old male who lived only a few days after admission to the hospital The diagnosis was lymphatic leukemia in the aleukemic phase, the white blood cell count was 4,600 Shorvan [221] described a 37 year old male who suffered from chronic myeloid leukemia The white count was as high as 354,000 Following x-ray therapy an acute attack of gout developed in the great toe The articular symptoms responded to colchicine McEwan [169] observed one patient whose symptoms of chronic myeloid leukemia covered a span of ten years The diagnosis of gouty arthritis was substantiated by the presence

of urate tophi. The white blood count was as high as 90,000 and the uric acid level as high as 13 6 mg.

We have recently reviewed the pathologic records of 91 cases of gout. There was one case of reticular cell sarcoma, two cases of myelofibrosis, one case of polycythemia without evidence of leukemia, one case of polycythemia with lymphatic leukemia, and two cases of polycythemia with myeloid leukemia. In this group there was no coexistence of myeloid leukemia and gout without predisposing polycythemia. At the Roswell Park Memorial Institute in Buffalo, a review of 168 cases of lymphatic or myeloid leukemia produced one case of clinical gout in the group.

The increased purine metabolism in leukemia may be considerably greater than that in patients with gout Ebstein[68] reported the excretion of more than 5 Gm. of urates in 24 hours in a patient with leukemia and gouty arthritis. In our study of one patient suffering from acute myelogenous leukemia without articular symptoms, we determined the metabolic pool to be approximately four times the normal size.[23] Yü and associates[283] studied the incorporation of N^{15}-labeled glycine in a patient suffering from polycythemia and recurring gouty arthritis with tophaceous deposits The protracted uric acid biosynthesis was presumed to reflect the augmented turnover of red cell precursor nucleic acids associated with increased erythropoiesis of polycythemia The peak of N^{15} concentration in the urine was considerably slower than that of either normal persons or of gouty subjects In contrast, Laster and Muller[146] observed a twofold increase of N^{15}-glycine incorporation into uric acid over a fifteen-day period in a patient with gout and myeloid metaplasia

A significant number of cases of non-leukemic myelosis, myelofibrosis or agnogenic myeloid metaplasia in association with gout have been reported[117, 141, 172, 254] Three cases in Hickling's report are noteworthy Case 1, a white female, age 65, had been aware of enlargement of the spleen for five years Postmortem examination showed a large amount of "yellow gravel in the right kidney." Undoubtedly, this was uric acid gravel which had developed as a result of the elevated uric acid content of body fluid The patient had suffered several attacks of acute gouty arthritis Case 2, a white male of 76, had complained of intermittent attacks

of classic gout for more than twenty years The liver and spleen were enlarged, the blood pressure was normal. It is believed that in this case gout was independent of the myelosis Case 3, a white male of 62, had suffered intermittent attacks of acute gouty arthritis for seven years Symptoms attributed to bone marrow depression were noted before the first attack of gout Subcutaneous tophi were present, from which uric acid crystals were obtained The patient responded well to anti-gout medication

Thirty patients with chronic myelosclerosis have been reported by Wyatt and Commers,[275] two of whom suffered from gout. Reifenstein[199, 200] has described a female with objective evidence of myelosclerosis who had been followed for eight years Symptoms of gout appeared five years after the basic diagnosis had been suspected The terminal blood uric acid level was 12 mg /100 ml and the non-protein nitrogen concentration was 27 mg /100 ml Pease[186] reported one case of a Negro farmer with myelonecrosis and gout The white blood cell count was 24,000 Three months after treatment was instituted to combat the blood dyscrasia, an acute attack of gout appeared X-ray examination showed osseous tophi in the great toe Weisberger and Persky[263] reviewed the records of 283 cases of lymphoblastoma seen at the University Hospitals in Cleveland over a period of ten years The incidence of uric acid calculi was 5 3 per cent in the series

Isolated instances of gout and multiple myeloma have appeared in recent medical literature[12, 221] Barr and associates[9] described one case of cryoglobulinemia and myeloma with acute gout which responded to colchicine The uric acid level was 11 8 mg and the blood urea nitrogen 43 mg Bronsky and Bernstein[41] reported an acute episode in the knee of a patient with myeloma A maximum concentration of uric acid of 17 0 mg was observed The diagnosis of gout was based upon the clinical characteristics of the inflamed knee, the elevation of serum uric acid, the recovery of uric acid crystals from the aspirated synovial fluid and a prompt response to colchicine

Other blood diseases associated with gout include pernicious anemia,[201] hemolytic anemia,[63, 144] Cooley's anemia,[162] purpura, hemophilia, erythronoclastic anemia,[144] juvenile poikilocytic anemia and nontropical sprue[177]

Diagnosis

In spite of gratifying progress in the understanding of the differential diagnosis of the several arthritis states, physicians have not yet reached the goal in this phase of medical practice. If a patient complains of joint distress, every effort should be made to identify specifically the type of arthritis responsible. Gout, a distinct clinical entity, should be differentiated clearly from the other articular disorders. In theory, the malady should not be difficult to suspect, but in practice, such is not the case. Nearly two decades ago Vorhaus and Kramer[259] estimated that an average of 8.8 years intervened between the onset of symptoms and the clinical diagnosis in 25 patients with gout. The current experience does not reflect consistent improvement in this regard. The following histories are not unique.

A. L., a 63 year old male, had an acute articular bout in the right great toe at the age of 30. Apparently his physician overlooked the fact that his mother and an older brother had gout. For a number [illegible] only mild [illegible] would be [illegible] tended per[illegible] [illegible] seventeen years after the first attack, his ailment was diagnosed as gout. [illegible] 1953, consultation was sought at which time, Cinchophen and sodium salicylate produced untoward reactions, and he "lived" on colchicine and aspirin intermittently, according to his story. Nevertheless, his condition became progressively worse, until in 1953, when his son, a medical student, suggested a regimen of colchicine 1.0 mg., and Benemid 2.0 Gm., daily. It has been approximately two years now since he has had even a threat of an acute attack. The tophus on his right ear has disappeared, and he is convinced that the tophi on his elbows and feet have decreased in size.

L. F., a 52 year old white male, was seen 15 years after his first attack in the right great toe. Because of a positive family history, a diagnosis of gout was considered in 1941, but the presumption was not pursued to a definitive conclusion. During the intervening years he suffered at least one attack of acute arthritis per year. Neither colchicine nor Benemid was prescribed during this period of time. Other anti-gout agents recommended were ineffective in producing relief. Early in 1956, after four attacks of acute articular distress, for the first time the diagnosis of gout was taken seriously.

Gout should be considered always in a case of unexplained acute arthritis in an adult male. "Confronted then, with the sus-

pected case of gout, whether acute or chronic, what shall be our way of approach? Not the easy and hazardous path of lightning diagnosis affected by those who plume themselves on their so-called clinical 'instinct,' but the slow, laborious route of clinical 'observation,' that leads more surely to the vantage ground of the truth, this assuredly in all disease, but in none more so than in joint disorders, whose outward resemblances so often hark back to inward disparities " This advice offered by Llewellyn [153] a generation ago, continues to be sound A presumptive diagnosis of gout may be confirmed by some or all of the several criteria The diagnosis is self-evident in the chronic tophaceous stage, but if identification has been delayed until this phase of the disease, the patient will have been denied specific treatment for a number of years Such a circumstance represents a failure for the physician and unnecessary distress to the patient The diagnosis should be suspected during the first attack of acute arthritis, although this may not be the first manifestation of the disease Other supporting items, anticipating the first attack, may suggest the presumptive diagnosis

Ancillary Items

A *family history* of gout should be interpreted as an omen, favorable, not sinister, to nonaffected relatives as well as to the family physician Careful inquiry should be made into the family history of every patient with unexplained acute arthritis If a family history of gout is obtained, even though it is one or two generations removed, this information is significant

An *increased concentration of serum urate* in a nonaffected relative of a gouty patient increases the probability of acute arthritis at some future time It is believed to be desirable for each member of a gouty family to undergo tests for such a determination periodically The individual should be recorded as a potential gouty patient with a low probability as determined by the isolated studies reported to date on this subject

A *urate calculus* may precede the initial attack of gout The percentage of patients with idiopathic urate lithiasis who subsequently develop acute gout, while not known, is presumably low There is a need for a long-term study of "idiopathic" urate stone formers in order to provide reliable data on this subject Now that

of uric acid in the serum greater than 6 mg/100 ml The upper range for normals in whole blood is somewhat less and the results are more erratic Most persons with a normal uric acid metabolism show a serum urate level less than 5 mg, in contrast to most gouty patients with levels usually higher than 6 mg There is a supplementary advantage, therefore, in using serum or plasma because of an intervening range of 1 mg. between 5 and 6, which separates most nongouty individuals from gouty patients Smyth and Huffman observed that 90 per cent of the patients with gout in their experience had a value greater than 6 mg [229] Hyperuricemia was present in 92 per cent of a series of 252 cases of gout reported from Spain [8] In our experience the incidence is greater than 95 per cent

The concentration of uric acid in the serum may be within the normal range in a bona fide case of gout if uricosuric agents have been administered prior to the collection of blood for the determination Patients with unexplained joint distress may receive one of a number of anti-arthritic agents, either on the advice of a physician or from their own medicine cabinet It is an interesting commentary in pharmacology that many of the nonspecific anti-arthritic agents have a uricosuric effect, while colchicine, the only specific anti-gout drug, has no demonstrable uricosuric action Cortisone and the newer steroids, ACTH, phenylbutazone, Benemid, salicylates and cinchophen are uricosuric drugs. If, perchance, sufficient amounts have been taken prior to the collection of blood, critical interpretation of the uric acid value is imperative. It is our practice to withhold any uricosuric agent for a period of at least 48 hours before obtaining blood if a control value is desired

On the other hand, the serum urate level may be elevated in a number of conditions other than gout Chronic glomerulonephritis, pyelonephritis, or other types of chronic renal disease, blood dyscrasias, and the lymphoblastomas may have an increased concentration of uric acid in the serum per se. Elevated levels have been observed sporadically in acute febrile illnesses, and poisoning by lead, ammonia, barbital, carbon monoxide or methyl alcohol [103]

The *response to colchicine* may be of diagnostic value as well as of therapeutic aid Colchicine is specific for acute gouty arthritis only and has little or no effect upon other forms of acute or chronic joint distress In a suspected case of gout, a full course of colchicine

should be administered as discussed in the section on *Treatment*. Most patients with acute gouty arthritis respond and the diagnosis is revealed. Since salicylates, steroids and phenylbutazone are non-specific anti-rheumatic agents, they are less useful, therefore, as a combined diagnostic and therapeutic guide. The exception may be phenylbutazone, which has been observed by some to be almost as specific as colchicine. Such has not been our experience. It should be stressed that if colchicine is prescribed as a diagnostic tool, full therapeutic amounts must be given. Inadequate amounts of colchicine may provide little symptomatic relief and may give, therefore, a misleading diagnostic answer.

Post-Attack Criteria

Following the successful termination of the acute attack, normal appearance and normal function return to the afflicted joint. The diagnosis between attacks in the absence of chronic tophaceous changes is neither less nor more difficult to make than during the acute attack. Each or several of the clinical findings noted above may be revealed in the procurement of the medical history. Except for the administration of uricosuric agents, the concentration of uric acid in the serum is elevated in the intercritical period.

There still remain two significant criteria, absent in the initial attack, but often present during the intercritical period after several years' course of the disease. These are subcutaneous tophi and osseous tophi. The deposits of urate may be rather extensive in the patient with moderate or severe gout but are not susceptible of detection until they have reached gross dimensions in selected soft tissues or in subchondral areas of bone.

The *urate tophus* in the ear, the hallmark of gout, does not appear in every patient suffering from this dyscrasia (PLATE XIV). The disease usually is well established when this stigma is noted. One or more white nodules on the helix of the ear is telltale evidence of the disease for a number of years as well as of neglect of earlier diagnosis. Patients with the severe form of the malady may have subcutaneous tophi adjacent to and involving most of the joints of the hands and the feet. The skin overlying a periarticular tophus may be bruised and urate sludge allowed to escape. The metatarsal phalangeal joints of the great toe, the terminal phalanges of the

fingers, the elbow, the knee, the lateral aspect of the foot and the heel are especially susceptible The Achilles' tendon is another area prone to attract urate deposits in a moderately severe case of gout

If confirmation of the presence of urate crystals is sought from a suspected urate tophus, there are several procedures available A tophus on the ear may be scraped by a hypodermic needle, or suspected urates recovered from a discharging sinus by a sterile swab If the recovered material is placed upon a microscope slide and viewed under a low-power lens, the characteristic needle crystals are readily identified. A suspected tophus that is removed surgically may be examined chemically for urates, as well as histologically, for structure after proper fixation. The colorimetric test for uric acid is accomplished by dissolving a small amount of urate sludge in distilled water and processing the solution, similarly to the handling of a sample of serum or urine. Although the identification of urates is described, this phase of diagnosis is old-fashioned. It is unnecessary to wait until the development of subcutaneous tophi to make a diagnosis of gouty arthritis

Roentgenographic evidence of gout in the bones of the extremities was demonstrated first by Huber[123] in 1896. The criterion which he considered characteristic of gout is the result of replacement with sodium urate of normal cartilage or bone. The loss of calcium leads to increased radiability of the involved areas Tophi must attain a considerable size, perhaps 5 mm. or greater in diameter, before they are visible by x-ray and their identity reasonably assured Since roentgenographic changes are not present in the early years of articular distress, several attacks of acute arthritis usually precede the development of roentgenographic changes A number of patients with a fairly long history of intermittent attacks may present normal roentgenographic findings in the affected parts A diagnosis of gouty arthritis in the intercritical period need not include roentgenographic abnormalities

Differential Diagnosis

In the differential diagnosis, several conditions simulatin[g] gouty arthritis should be considered. The commoner forms o[f] articular disease present the principal diagnostic difficulties. Becaus[e] acute rheumatic fever may resemble acute gouty arthritis, the physician may find the task of differentiation, in the case of a young person, assuming formidable proportions in the initial examination. Either condition has a predilection for the peripheral joints. Symptoms may appear rather suddenly following a streptococcal infection. Cardinal signs of inflammation of one or more joints, as well as manifestations of a systemic process, may be present. An increased sedimentation rate and an exacerbation following a surgical operation are not distinguishing features. Since gouty arthritis may appear in young persons, while acute rheumatic fever may appear in older individuals, the diseases are not mutually exclusive insofar as age of onset is concerned. A favorable response to ACTH or salicylates may not be diagnostic of either malady, nor the level of uric acid in the serum determinative. A few patients studied on the medical service with typical rheumatic fever have had an elevated concentration of serum urate. This elevation has been interpreted as a manifestation of stress.

In contrast, the articular distress usually is more acute in gout, and the distribution between sexes is dissimilar. While acute rheumatic fever has a slightly higher incidence among females, gout is predominantly a disease of males. Cardiac complaints and characteristic electrocardiographic changes, likewise, suggest rheumatic fever. A response to colchicine is characteristic of gouty arthritis. X-ray films of the affected joints in acute rheumatic fever show soft tissue swelling only.

A history of acute rheumatic fever or the presence of rheumatic valvular heart disease in patients with well-defined gouty arthritis has been of some interest to us in recent years. It may be only chance that an occasional patient with gout will have had rheumatic fever as a child. A more probable explanation is the incorrect diagnosis of rheumatic fever; very likely the joint symptoms were the clinical manifestation of the initial attack of gout. On the other hand, a more than casual relationship between rheumatic fever

gouty arthritis has been implemented by postmortem findings in gouty patients A review of a series of postmortem studies on gouty patients from a number of hospitals revealed several examples of garden-variety rheumatic valvular heart disease In the history of patients being followed regularly in this clinic, there are three instances of rheumatic valvular heart disease and two additional patients who gave a past history of rheumatic fever as a child or young adult, without clinical evidence, subsequently, to support a diagnosis of rheumatic valvular heart disease

Rheumatoid arthritis should not present a diagnostic problem except in unusual circumstances (PLATES XV AND XVI). As has been stated, females are particularly prone to rheumatoid arthritis, not to gout In the former condition, the joints tend to be involved symmetrically and usually without the sudden onset of articular distress Although the average age of onset is similar in rheumatoid arthritis, the duration of a single attack is much longer, and constitutional symptoms such as malaise, anorexia, weight loss and vasomotor changes usually persist In the infrequent cases of the coexistence of gout and rheumatoid arthritis, the diagnostic problem becomes doubly perplexing Patients who have presented these baffling symptoms usually have been males in the fourth or fifth decades of life (FIG 41)

Roentgenographic changes in rheumatoid arthritis may be confused with those of gout. The cystic areas in rheumatoid arthritis however, tend to be more centrally located, such as in the metacarpals or the carpals The hands and wrists (FIG 42) are affected more often than the feet and ankles Frequently, generalized decalcification is apparent in rheumatoid arthritis if cystic changes are demonstrated (FIG 43) On the other hand, generalized decalcification in gouty arthritis is unusual The differential diagnosis of rheumatoid arthritis versus gouty arthritis or the coexistence of these two conditions may be resolved only by a biopsy of a nodule or the synovial membrane of the joint under scrutiny A rheumatic nodule is readily distinguished histologically from a urate tophus Read and Burton [197] have described a case of ankylosing gouty arthritis that simulated rheumatoid arthritis Joint biopsy confirmed the diagnosis of gout After more than three years of incapacity because of fixation of several large joints, an anti-gout regimen was instituted with

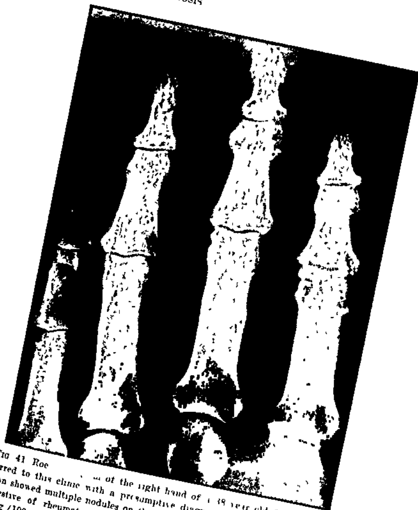


Fig 41 Roe[illegible]m of the right hand of a 38 year old female who was referred to this clinic with a presumptive diagnosis of gout Physical examination showed multiple nodules on the hands, feet and elbows that were highly suggestive of rheumatoid cysts The concentration of serum uric acid was 3 4 mg/100 ml A number of the subcutaneous nodules were removed surgically Microscopic examination confirmed the diagnosis of rheumatoid arthritis The X ray films of the hands show areas of bone destruction involving the lateral portion of the metacarpal heads with minimal changes in the phalanges There are many soft tissue nodules about the interphalangeal joints (See Fig 27)

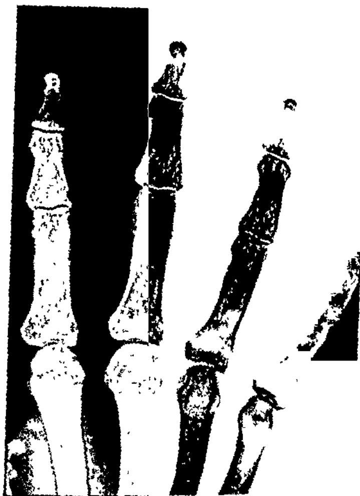


FIG. 42 Roentgenogram of the right hand of a 44 year old male who has suffered from crippling joint disease for more than four years. Gout was suspected and the patient was referred to this clinic. The physical examination revealed changes typical of rheumatoid arthritis. The concentration of serum uric acid was 3.4 mg./100 ml. A biopsy of one of the nodules confirmed the clinical impression X-ray examination of the hands showed the characteristic findings of rheumatoid arthritis as well as sclerotic lesions of the tufts of the distal phalanges. The calcified tufts are similar to those observed at times in patients with Raynaud's syndrome. This is not calcium gout



FIG 43 Roentgenogram of the left hand of a 57 year old male who had suffered three acute attacks of gouty arthritis between 1939 and 1946 In 1954 he developed symptoms typical of rheumatoid arthritis When he was seen in 1956, well developed chronic deforming changes of rheumatoid arthritis were present in the various joints of the body The concentration of the uric acid in the serum ranged from 7 2 to 9 0 mg /100 ml X ray studies show changes of the proximal phalangeal joints, subchondral sclerosis, nonspecific cystic changes in the head of the first metacarpal, the right second metacarpal head and the carpal bones None of these findings is typical of osseous tophi



Fig 44 Roentgenogram of the left foot of a 52 year old male who had experienced intermittent attacks of acute gout for twelve years The concentration of uric acid in the serum was 11 6 mg /100 ml. The blood pressure was normal Evaluation of cardiac and renal function revealed normal values There are good pulsations in the vessels of the feet. Multiple, sharply defined, punched out areas along the lateral surface of the head of the first metatarsal are apparent These changes could be attributed either to osteoarthritis and hallux valgus or to gout

impressive clinical results At the last report the patient was ambulatory and able to drive an automobile

Patients with rheumatoid arthritis and with little to suggest gouty arthritis may show some increase in the concentration of uric



Fig 44 Roentgenogram of the left foot of a 52 year old male who had experienced intermittent attacks of acute gout for twelve years The concentration of uric acid in the serum was 11 6 mg /100 ml. The blood pressure was normal Evaluation of cardiac and renal function revealed normal values There are good pulsations in the vessels of the feet. Multiple, sharply defined, punched out areas along the lateral surface of the head of the first metatarsal are apparent These changes could be attributed either to osteoarthritis and hallux valgus or to gout

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Patients with rheumatoid arthritis and with little to suggest gouty arthritis may show some increase in the concentration of uric



FIG 46. Roentgenogram of the hand, showing an enchondroma in the head of the second metacarpal bone (See FIG 20)



Fig 47. Roentgenogram of the wrist, showing an enchondroma in the head of the radius. (See fig. 25)

acid in the serum In addition to our own observations of this increase from time to time, it has been brought to our attention recently by Bunim [45] as follows "We have now collected six patients with hyperuricemia who have been diagnosed on clinical grounds as having rheumatoid arthritis, yet on biopsy of the synovial tissue,



FIG 48 Roentgenogram of the left hand of a patient with fibrous cystic dysplasia. (See FIG 21)



FIG 49 Roentgenogram of the ankle of a patient with neurofibromatosis There are cystic changes in the fibula (See FIG 24)

it was discovered that they had unequivocal gout This finding of course, raised the question as to the frequency of hyperuricemia in rheumatoid arthritis Finding no good data in the literature and after writing to several colleagues, I received one reply relating that 20 per cent of patients with rheumatoid arthritis exhibit hyperuricemia ''

Osteoarthritis, or degenerative joint disease, may be confused with gouty arthritis, particularly in patients over 50 years of age Acute articular episodes are uncommon in patients with degenerative joint disease, although an acute Heberden's node is somewhat suggestive of a small gouty tophus, both in location as well as in



FIG. 50 Roentgenogram of the foot of a patient with blastomycosis (See FIG. 58)

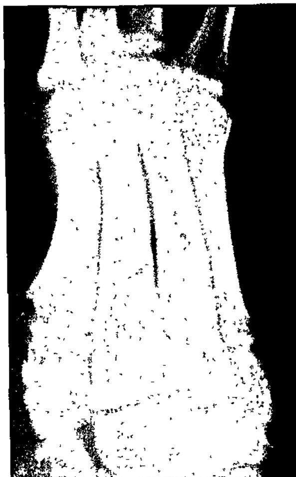


FIG 51 Roentgenogram of the foot of a patient with leprosy There is destruction of the shaft of the fourth metatarsal

associated symptoms A quiescent Heberden's node should not be mistaken for a tophus Females are more prone to the development of Heberden's node than are males, and acute articular episodes are uncommon in patients with osteoarthritis As a manifestation of the aging process, it is not surprising that clinical and roentgenographic evidence (FIG 44) of osteoarthritis appears frequently in patients with gouty arthritis past the age of 50 The response to antigout measures should be reassuring in spite of the presence of degenerative joint changes

In a previous treatise on the subject of gout by the author,[240] mention was made of gonorrheal arthritis, acute specific pyogenic arthritis, and cellulitis of the periarticular spaces, maladies that should be considered in the differential diagnosis The widespread use of antibiotics, however, has largely eliminated these three possibilities In the course of acute gout, antibiotics seem only to aggravate the condition If the articular disturbance is specifically infectious in etiology, however, antibiotics may be responsible for rapid subsidence of symptoms

A differential diagnosis of gout by x-ray examination of the extremities may include unusual conditions such as bone atrophy associated with infection and neuropathy (FIG 45), enchondromata (FIGS 46 AND 47), fibrous cystic dysplasia (FIG 48), neurofibromatosis (FIG 49), blastomycosis (FIG 50) and leprosy (FIG 51).

Prognosis

THE PROGNOSIS IN GOUT is more satisfactory than in any other of the potentially crippling types of joint disease This statement appeared to be valid to the author more than a decade ago, and in spite of major advancements in the management of several types of joint disease, the prognosis in gout has not lost its relative, favorable position This status is directly related to progress in management, a topic to be discussed in the appropriate section

Prior to the last few years, it was generally accepted that the more frequent the acute attacks, the more rapid the progression of the disease and the greater the probability of the development of chronic deforming changes This view was believed to be particu-

larly applicable to the gouty patient in whom the onset of articular distress occurred in adolescence or early adulthood. Patients who experienced the onset of articular symptoms in the declining decades of life usually escaped chronic tophaceous gout. Furthermore, it was speculated that the larger the metabolic pool, the greater the tendency for the early onset of articular symptoms and the more extensive the deposition of sodium urate in and about the joints. While, at the present time, factors contributing to the size of the metabolic pool are not susceptible to alteration by available agents, clinical effects of the increased metabolic pool may be modified significantly. Contemporary optimism in prognosis should be of great solace to the afflicted. A case report is illustrative.

M.M., a 44 year old physician, had endured acute attacks of gouty arthritis for more than 14 years. He was seen in this clinic first in 1952. During the preceding two years he had suffered increasing disability and eventually had become so discouraged that he had decided to abandon the practice of medicine and had permitted the lease on his office to expire. On physical examination he had a flexion deformity of the left knee with apparent fixation at an angle of almost 45 degrees. The concentration of uric acid in the serum ranged from 8.8 to 10.2 mg./100 ml. Under orthopedic supervision the deformed leg was straightened and placed in a cast. Daily medication included colchicine and Benemid. Rehabilitation, carried out gradually during the following weeks achieved a normal gait three months later. Resuming the practice of medicine within six months, he has since continued it without interruption. This physician has been incapacitated less than one day per year because of acute gouty arthritis during the past three years. Benemid and colchicine are ingested daily.

The discussion of prognosis above is invalid in patients with severe renal disease. Uremia is the determining factor in a few patients. Gudzent[101] stated that "Prognosis in gout depends solely upon the state of the renal vessels." Critical renal impairment may be unrelated to the severity of chronic tophaceous arthritis and, in a few patients, may lead to premature death. Three examples of death from uremia are given. The first and second patients had minimal joint distress, the third, extensive tophaceous gouty arthritis.

G.E., a 54 year old male, suffered from intermittent mild attacks of acute arthritis for more than 15 years. The articular affliction was of moderate degree only, and physical examination revealed no evidence of chronic deforming gouty arthritis or subcutaneous tophi except in the ears

The patient was followed in this clinic for more than six years with persistent hypertension and persistent retention of nitrogenous products (FIG. 40). The articular symptoms were kept under control with colchicine and Benemid. Death occurred from uremia in 1955.

Kahn and Dixson have reported a similar example.[134]

A 57 year old male with a blood pressure of 220/130 suffered episodes of acute gouty arthritis for a number of years, and documented nitrogen retention for six years There was no evidence of osseous or subcutaneous tophi

K H , a 48 year old female, died with renal insufficiency, having experienced acute attacks of gouty arthritis since the age of 14 [56] For more than a decade before death, subcutaneous tophi were present, and evidence of renal impairment had been detected more than five years before death At that time x-ray examination of the hands and feet showed extensive osseous tophi, the specific gravity of the urine was fixed at 1 010, the P S P excretion was markedly depressed and significant amounts of albumin were detected in the urine Repeated bouts of acute gout were difficult to control with colchicine She died in uremia.

These cases lend little support to the belief that clinical evidence of renal impairment is a direct function of the severity of articular gout. Additional factors, presumably influencing progression and severity of renal dysfunction, include pyelonephritis, unrelated vascular disease in the kidneys, amyloid deposits in the renal parenchyma and other less well-defined forces. What is the prognosis in patients with gout if renal impairment is co-existent? Surely the prognosis is better in a patient with demonstrable renal disturbance from gout than is the prognosis in a similar disturbance associated with chronic glomerulonephritis. The presence of albuminuria, impaired concentrating ability and impaired ability to excrete phenolsulfonphthalein dye without any recognized cause other than the possibility of chronic glomerulonephritis justify a grim outlook. If the diagnosis of gout is warranted as an explanation of these findings, the prognosis is considerably better. Also, the prognosis of complications from hypertension, particularly in a male, is less grim if gout is present It is believed that hypertension and gout make for a better prognosis than does hypertension without associated gout

Prevention

THE PREVENTION OF the disturbance of uric acid metabolism i beyond the realm of present-day medicine. There is one notewort phase of this category, however, i.e., the identification of hype uricemic members of gouty families. Recognition of these member marks the first step in the clinical control of gouty arthritis. Th practice of determining the concentration of uric acid in the serum of each relative of a gouty patient was started a number of years ago in our clinic as discussed in the section on *Heredity*. In selected instances, the information obtained has proved of considerable value.

The development of acute attacks of gout in hyperuricemic individuals is so infrequent as to render unnecessary specific therapy prior to the initial articular episode. While waiting for the slight probability of the initial attack of gout, the family physician should not overlook the identification of hyperuricemic individuals. Probably the most important item is the identification of potential gouty patients so that the correct diagnosis will be made at the time of the first attack and appropriate management recommended. Also, it is believed that the diagnosis of gouty arthritis should not be withheld from other members of the immediate family. Members of the present generation appear eager to be informed on many aspects of modern medicine. Since great strides have been taken in the management of gout at the present time, optimism, rather than fear, should accompany the dissemination of information in a family afflicted with the malady under discussion.

Treatment

THIS IS THE MOST REASSURING SECTION of any to discuss. If a correct diagnosis has been made and gout is responsible for the articular distress, proper treatment will be rewarding, both to the patient and to the physician. Although gout is a chronic disease with a tendency for articular symptoms to remain in each susceptible individual, irrespective of the efficacy of therapeutic agents, richer dividends may be anticipated in the treatment of gouty arthritis than in any other major type of joint disease. The appreciation of this potential continues to be overlooked by many physicians. In spite of reiteration by those especially interested in this malady, a number of qualified physicians either profess ignorance of the therapy of gout or have an unconscious reluctance to accept fully the therapeutic armamentarium now available. Equally important is the need for the physician to impress upon the patient the desirability of unceasing adherence to this prophylactic regimen, in order to prevent, abort or reduce in incidence, acute episodes.

Since gout has been recognized as a clinical entity for many centuries, there has been a tendency for therapeutic measures, in the main unsatisfactory, to be handed down from teacher to pupil with little or no modification. The admonitions of 50 years ago regarding dietary restriction in gout have been modified but slightly in several current textbooks of medicine. Some supposedly anti-gout drugs are in a similar category as are, to a lesser degree, mineral waters and mineral baths.

Undoubtedly, a portion of the blame rests upon those who are responsible for the teaching of arthritis in medical schools and in hospitals. Lack of interest in the several arthritides by teachers of medicine is apparent to many critical observers. Until recently, a defeatist attitude on the part of the physician, and shared by the patient himself, kept the subject of joint disease, including gouty arthritis, from receiving much attention in the medical curriculum. Because of several effective forces, however, this point of view is losing ground and may in the future be replaced by putting the proper emphasis upon diagnosis and treatment of the several common types of arthritis. In this utopia an appreciation of the importance of proper management of gout will insure each afflicted

patient the benefits now so often denied because of unintentional omissions

Although acute articular symptoms of gout have responded for centuries to colchicum or colchicine, clinical science has so far failed to take full advantage of this specific pharmacologic agent. Because of the lack of understanding of the therapeutic value of colchicine, some physicians shun its use Furthermore, during the past two decades, the use of colchicine in the intercritical or prophylactic period has found too few staunch supporters Yet another factor has been responsible in recent years for confusion in the selection of drugs for the proper management of the acute attack as well as for the intercritical period The initial enthusiasm that accompanied the clinical trial of cortisone and ACTH in the treatment of acute gouty arthritis shifted, shortly after, to phenylbutazone and, more recently, to Colcemide Glowing reports of the efficacy of each substance have tended to confuse the practitioner rather than to guide him While each of these has merit, no one preparation has supplanted colchicine in the management of gouty arthritis

A few remarks regarding therapeutic evaluation are pertinent before a detailed discussion of therapy Perusal of the literature reveals an extensive array of diets, regimens and sovereign remedies that have been recommended for the treatment of one or more phases of gouty arthritis Probably the number is no greater than may be recorded for rheumatoid arthritis or for osteoarthritis, conditions for which no specific therapy is available, the implication being that the number of recommended regimens merely reflects the failure of any one to be specific and effective The fact remains that the number for gout is appreciable in current literature Are we then justified in tagging the physician recommending a particular measure as a biased observer? No! He does not deserve to be so maligned, but he may justly be suspected of lack of awareness of the variations in incidence, duration and severity of the acute attack or the probability of development of chronic deforming changes Since the disease is variable and follows a pattern neither consistent nor regularly predictable, it is hazardous to attribute benefit to a particular procedure or drug in any gouty patient unless an adequate history has been documented for several years Equally hazardous is the prediction of duration and severity of an individual

attack in a gouty patient in the initial stages of an acute episode. If the experienced physician sees the patient during the first hour of an acute attack of gout, he will be conservative in prognosticating the severity or the duration of the seizure. Some patients may sense the difference between a mild and a severe attack shortly after the development of symptoms, but they too may withhold judgment if they have experienced several acute bouts Thus, unless the patient and the physician, respectively, are thoroughly familiar with the course of previous acute attacks, fallacious deductions may be drawn regarding a single therapeutic procedure.

The evaluation of measures thought to be beneficial in the prophylactic period is as difficult as during the acute episode There is no infallible formula for determining the duration of the interim period If the patient with gout seeks medical advice, follows it, and has no articular distress for a year or more, naturally both the physician and the patient assume this freedom from distress to be the direct result of the therapeutic agents and regimen It is not always appreciated that the patient might have experienced a similar period, free from acute symptoms, without recourse to specific measures, provided inciting factors were absent. It is particularly important, therefore, to discuss the therapy of the intercritical period in terms of years rather than in shorter periods of time, to obviate the danger of the *post hoc, ergo propter hoc* fallacy.

The management of the prophylactic period will be considered first, because it is believed that prevention of acute attacks should *take precedence* Although the acute episode is a miserable affair if allowed to reach full proportions, proper respect for the intercritical regimen may reduce the incidence of acute attacks to clinical insignificance

Intercritical or Prophylactic Period

The greater portion of the time of the patient afflicted with gout should be intercritical, i e, the period between acute episodes The recommended prophylactic regimen is simple to follow, permits the patient to live essentially a normal life and either stays or reverses the previously progressive effects of the disturbance of uric acid metabolism. Percentagewise, the days or hours per year squandered because of acute symptoms should be insignificant.

Considerable progress has been made in the understanding of the pathogenesis of the uric acid disturbance Greater benefits may be recorded, however, in the prevention of the recurring attacks through the judicious management of the intercritical period. The direction of this phase of gouty arthritis is concerned largely with the regular administration of two of the most effective anti-gout agents, i e, colchicine and Benemid Although each is essential to the regimen, it is the synthesis of the combination that is responsible for the excellent clinical results. Each drug complements the other; neither one by itself is so effective The other anti-gout agents may be disregarded in prophylaxis if colchicine and Benemid are taken regularly While the use of colchicine regularly as a prophylactic agent is not new, the discovery of the uricosuric action of Benemid and the acceptance of this agent is new In fact, it represents a significant advance in the treatment of a chronic disease and may be regarded as one of the important new agents made available through modern chemical and clinical investigation *Regardless of the fact that colchicine and Benemid will be considered individually, their value in the clinical management of gouty arthritis embodies the synthesis of the combination*

Ring[202] was one of the first clinicians to describe the interval use of colchicum "He now takes 11 drops of the eau médicinale every night at bedtime he lately assured the author of this treatise, that for the space of 15 months, since he began to take the medicine, he has never been confined a single day, that his health is regularly improving " Gairdner[85] also noted "He was taking 20 minims of Vin Colchici, four times a day and had done so for a long time " Garrod[90] also recommended colchicum as a prophylactic agent "There is some evidence and considerable authority for regarding colchicum as effectual in warding off an attack of gout, especially when an approaching fit is beginning " In 1936 Cohen[55] advocated the intermittent use of colchicine This procedure was broadened by the author in 1938 to embrace continuous prophylactic therapy[241] "Many of the patients in our series who have more than two attacks of gout a year are given three tablets of colchicine each day for two or three days each week The use of colchicine in this amount in several cases for more than two years has not produced any recognized toxic symptoms and we believe that

it is a safe practice " A stronger statement [240] was made in 1943: "Some colchicine should be prescribed in symptom-free periods to most gouty patients This habit may vary from not more than one or two tablets a week to a daily ration of from one to three tablets "

The daily use of this preparation in the intercritical period has been found to be extremely useful, although little or no effect

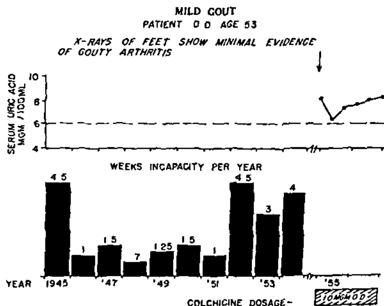


FIG 52 Experimental observations on a 53 year old male who has suffered from mild gout since 1945 Weeks of incapacity before beginning colchicine are charted No time was lost from work during a period of two years after beginning colchicine

upon uric acid metabolism may be attributed to colchicine (FIGS 6 AND 52) It is a good practice to recommend some colchicine regularly as a prophylactic to each patient with gout. Having used colchicine in such a manner for almost two decades and in recent years in conjunction with Benemid, I am thoroughly convinced of its efficacy as a prophylactic preparation and believe that its effectiveness, combined with negligible toxicity, places it in the superior category One 0 5 mg tablet is recommended three or more

days each week in mild cases with a past history of not more th one attack per year Patients moderately afflicted should take o or more colchicine tablets each day of the year The severe afflicted should take colchicine day in and day out up to the limi of gastrointestinal tolerance The subtoxic level may be two or thre tablets daily A few patients may tolerate as many as four tablets daily year after year Not more than 5 per cent of the patients seen by the writer require such a quantity of colchicine Approximately two-thirds of the patients in our series take one or two colchicine tablets only each day A minority, but a somewhat larger number than those severely afflicted, take a few tablets each week or a few tablets each month I am not aware that any patient in our series goes for any significant period of time without taking a few colchicine tablets

The results of this recommendation, when combined with Benemid, as noted below, leave no doubt of its value The incidence of acute attacks was reduced through the prophylactic use of colchicine alone before Benemid became available The combination has resulted in a further reduction in the incidence of acute attacks and an improved state of well-being It is my conviction that the periodic use of colchicine between attacks is a beneficial anti-gout measure and is not harmful Intolerance to the drug does not develop and when an acute attack appears, a full course of colchicine is maximally effective, irrespective of previous ingestion This is an important clinical observation and should not be forgotten by patient or physician Prescriber and recipient of drugs frequently believe that continued use eventually results in habituation or intolerance Either possibility is valid for many drugs, but not for colchicine (or Benemid) The only exception to this statement is the circumstance in which the susceptible person is on the borderline of gastrointestinal irritability from the daily ingestion of colchicine A full course may not be tolerated in such an individual because of the premature appearance of nausea, vomiting or diarrhea Patients who have been on daily rations of colchicine for a decade or more receive the optimum benefit from a full course when this is prescribed Hence, it is important that the quantity of colchicine ingested daily be maintained at a level that will not compromise the intestinal tract

In view of the satisfactory history of many patients rem

taking colchicine for a decade or more, we may pronounce such a regimen beneficial and associated with no undesirable features if gastrointestinal symptoms are avoided during the prophylactic periods Another obvious gain in the ingestion of colchicine regularly is the advantage of having started a course at the earliest possible moment, should acute symptoms appear. A patient should never be without a vial of colchicine tablets A supply should be available at home, at the office and in the traveling case The age of the patient is no contraindication to the periodic use of colchicine. Until such a time as more effective drugs are discovered or more effective means of correcting the disturbance of uric acid metabolism are devised, it is believed that colchicine and Benemid should be the foundation stones of the prophylactic regimen and thereby provide protracted periods of freedom from acute symptoms and make prophylaxis factual.

Colchicine stood alone as the prophylactic drug of preference in the intercritical period until recently and lacked a companion preparation which possessed a persistent and powerful uricosuric action endowed with the property of correcting the dysfunction in uric acid metabolism Prior to 1950, reliance had to be placed upon salicylates or cinchophen for a uricosuric effect. Each preparation is moderately analgesic as well as moderately uricosuric The analgesic action in the intercritical period should not be required, and the uricosuric action of either agent left much to be desired Furthermore, cinchophen gained a bad reputation because of its toxicity and was held responsible for a number of cases of acute liver atrophy. The toxicity of salicylates does not pose a serious clinical problem, but most investigators have found it to be a weaker uricosuric agent than Benemid.

Benemid was first made available for clinical trial[104, 245] in 1950 Selected patients with a long history of intermittent attacks of severe gouty arthritis, as well as others with a milder form of the disease, were placed on Benemid initially and have taken Benemid daily for more than six years More patients were placed upon it as our confidence in the drug increased, and eventually almost all patients suffering from moderate or severe gout were prescribed Benemid Some of the mildly afflicted were given Benemid plus colchicine; others were continued on colchicine only as controls,

irrespective of the severity of the disease. It should be noted that colchicine was continued regularly as it had been in the past or, if the patients were seen for the first time, colchicine was incorporated into the regimen We do not have any patients who have been on Benemid only without colchicine, nor do we propose to obtain such clinical data since the results of colchicine plus Benemid are to us definitive A few examples of patients receiving Benemid only, on the advice of their family doctor, have been brought to our attention The singular use of this drug has occurred through misconception on the part of the physician or of misunderstanding by the patient The uricosuric action undoubtedly has been operating, but no change in incidence of acute attacks has resulted in the relatively short time that the inadequate regimen has been followed Undoubtedly, the incidence of acute attacks would have been influenced if Benemid, without colchicine, had been continued for a longer period of time We prefer to take full advantage of the combination of colchicine and Benemid once the diagnosis of gout is made

The dose of Benemid recommended has been decreased somewhat as we have gained additional experience Initially a few patients were placed upon 3 Gm of Benemid daily This was soon found to be an excessive dose and produced gastrointestinal distress Thereafter, those patients severely afflicted were prescribed 2 Gm of Benemid daily Those moderately or mildly afflicted were prescribed 1 Gm a day We proceeded originally on the assumption that the larger the quantity of Benemid ingested, the greater the uricosuric action and the greater the inhibition of the tendency to urate precipitation in bony and soft tissues This assumption still appears to be sound theoretically, but clinical experience has been almost as satisfactory with subheroic doses Throughout the high dose regimen, the value of a high fluid intake in order to inhibit precipitation of urates in the renal tubules, was stressed Except for the desirability of keeping the dosage of any medication as low as is consistent with optimum benefit, there appears to have been no dire consequences and no untoward symptoms, except gastrointestinal distress, associated with the larger amounts

The clinical benefit that accompanies the administration of Benemid becomes increasingly more encouraging year by year There are two actions that may be attributed directly to Benemid,

and two actions to the combination of colchicine and Benemid An increased excretion of uric acid in the urine and a decreased concentration in the serum is the anticipated effect of Benemid A maximum change occurs at a given dose level within a few days after beginning medication (FIG 7 AND 53) Thereafter, equilibrium tends to be established and maintained year by year. The majority of patients experience a significant decrease in the concentration of uric acid in the serum This ranges from 20 to 40 per cent when

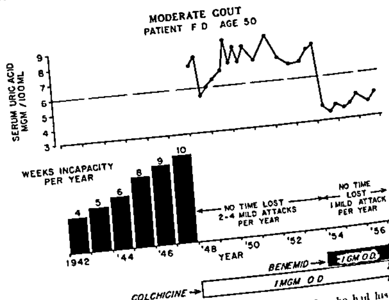


FIG 53 Experimental observations on a 50 year old male who had his first attack of gouty arthritis in 1942 The observations were made before and after prescription of anti gout agents

2 Gm of Benemid are ingested daily, and a slightly smaller effect when the Benemid dose is less Not more than 10 per cent of the patients in our experience who take 1 Gm or more of Benemid have failed to show a significant decrease in the concentration of uric acid in the serum Since those failing to respond have enjoyed normal renal function one cannot attribute the lack of response to failure of the kidneys to excrete uric acid under the usual uricosuric

stimulus Even the patients who have not responded with a significant decrease in the uric acid level have shown a clinical response, nevertheless This fact leads us to believe that Benemid is accomplishing some good, even though this good cannot be confirmed by the biochemical determinations The ultimate level on Benemid averages 6-8 mg /100 ml if the level of uric acid in the serum is

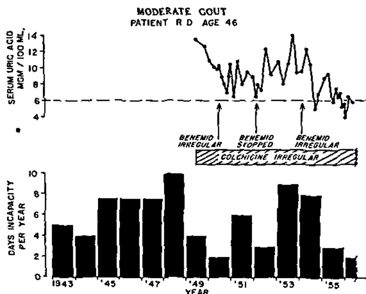


FIG 54 Experimental observations on a 46 year old patient with moderately severe gout, who responded poorly to the colchicine Benemid regimen There was considerable doubt as to the quantity of anti gout drugs taken daily by this patient

in the high gouty range, i e, 8-12 mg /100 ml (FIG 54) If the uric acid disturbance is milder and the serum urate concentration lower, the uricosuric action of Benemid reduces the level to the normal range, i e, 4–6 mg (FIG 55) It should be emphasized that each of our patients is on a balanced diet without restriction of protein intake Only those foodstuffs high in purine substances such as liver, kidneys, sweetbreads and anchovies are prohibited Un-

doubtedly, a rigid protein restriction, when combined with Benemid, would produce more favorable laboratory data, but I doubt whether the clinical results would be improved significantly It should be stressed that, irrespective of the severity of the disturbance, the action of Benemid is apparent. Unfortunately, because of the transient effect upon the alteration of uric acid metabolism, with-

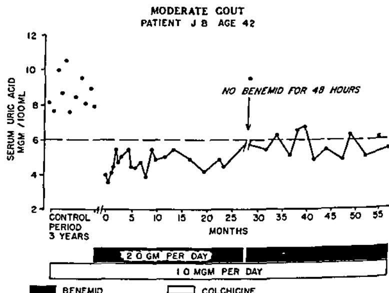


Fig 55. Experimental observation on a 42 year old patient afflicted with moderately severe gout over a period of eight years The concentration of serum uric acid as a function of Benemid ingestion is illustrated

holding Benemid experimentally or unintentionally causes a prompt return of the serum urate level to the pre-Benemid value. This reaction does not indicate a nullification of the benefits of Benemid therapy but rather underlines the chronic nature of the disturbance and allows the reaccumulation of urates in the tissues to begin anew with the cessation of Benemid.

The second direct effect of Benemid is the decrease in the size of subcutaneous tophi[190] and recalcification of the punched-out areas in the bone, areas of urate deposition which have slowly re-

placed calcium salts Two series of x-ray films which illustrate these changes will be presented below. There are no illustrations of regression of subcutaneous tophi Excellent illustrations of this phenomenon, however, are presented by Gutman [106] It continues to be our practice, if large subcutaneous tophi are present on exposed portions of the body, to remove them surgically rather than to wait for Benemid to reduce them gradually The cosmetic effect is

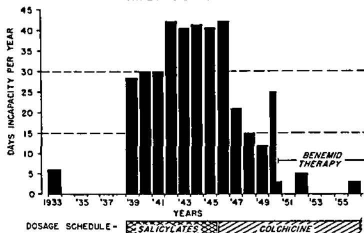


FIG 56 Experimental observations on a patient afflicted with severe gouty arthritis over a period of twenty five years For more than six years the patient has been on the colchicine Benemid regimen and has not lost any time from work because of acute gouty arthritis

achieved immediately, and the possible added load upon the kidneys in excreting this excess uric acid is eliminated

The most important subjective evidence of the combination of Benemid and colchicine is the diminution or elimination of acute attacks of gout Acute attacks have appeared at times in some of the patients irrespective of the length of time that they have adhered to the colchicine-Benemid regimen (FIG 56) It is mildly discouraging to the patient, as well as to the physician, to observe an acute

attack during the first few weeks on the prescribed regimen Originally it was our impression that there was a slightly increased incidence during the first few weeks or months after beginning Benemid Lacking confirmation of this impression in subsequent experience, we question the cause and effect in the matter of attacks after beginning Benemid Possibly these attacks would have occurred in any case The appearance of acute attacks while on a uricosuric agent with a normal level of uric acid in the serum is an interesting observation and confirms the impression stated some years ago that the absolute level of uric acid in the serum is not the determining factor in the etiology of the acute attack of gout From four to six months after beginning the prophylactic regimen, there is an unchanged or slightly decreased frequency of attacks Thereafter, the marked diminution in incidence is gratifying. A number of patients on colchicine and Benemid for a period as long as six years, with a past history of moderate or severe gouty arthritis, have not lost a day from work in recent years because of acute gout (FIG 57) A majority of patients, irrespective of the severity of the disease, average less than one day per year of incapacity because of acute arthritis This fact represents a striking change from the inciden of attacks before beginning the combined therapy.

Another effect of the combined medication is an improved feeling of well-being, not noted while colchicine was the only drug administered regularly Undoubtedly, this euphoria is associated with a reversal of the migration of urates from body fluids to bones and soft tissues Because of the beneficial features of an abundant fluid intake for most patients with gout, under a Benemid regimen, this aspect of treatment should be stressed Since the concentration of uric acid in glomerular filtrate is near the saturation level, every effort should be made to provide an abundance of fluid for the kidneys in order to prevent precipitation of urates in the tubules

The incidence of toxicity and the number of patients who are forced to discontinue Benemid is unimportant clinically. Bone marrow depression or liver damage has not been observed [106] The incidence of renal stones, as noted in the section on *Pharmacology*, is believed to be unaltered during the combined therapy. Gastrointestinal distress may be prevented by the ingestion of Benemid with meals Two patients developed a skin rash after beginning

Benemid One of them, refusing to hold the drug responsible, continued to use the drug The rash never became a serious matter and has not prevented the continuation of Benemid for more than four years The second patient developed pruritis shortly after beginning the ingestion of 1 0 Gm of Benemid daily The side effects subsided with cessation of the drug and the institution of

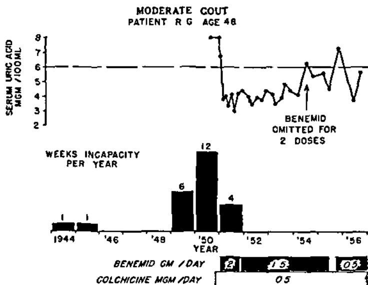


Fig 57 Experimental observation of a 48 year old patient with moderately severe gout since 1944 There has been no time lost from work because of acute attacks of gouty arthritis since beginning the colchicine Benemid regimen

an antihistaminic preparation Benemid was resumed later without incident During the six years of experience with combined therapy, only three patients in a group of approximately 150 have discontinued Benemid permanently because of presumptive or real side-effects The first patient was 75 years of age (FIGS 29 AND 30) He was mildly afflicted with gout and took the new drug for a few days only As best I could determine, he discontinued the Benemid because he didn't think it was necessary He continues to take

colchicine, has a mild form of gout and has had only one attack of acute gout in the past five years Probably his judgment was sound in not continuing Benemid at his age. The second patient was a physician, 82 years of age when first seen He suffered from mild gout. He is now 86 years of age and has had no attacks in recent years When gastrointestinal irritability developed on 2 Gm. of Benemid daily, he discontinued the medicine without consultation In spite of the gastrointestinal distress he maintained that he felt better generally during the weeks that he was taking Benemid Nevertheless, he did not resume medication Another patient, noted in our previous monograph on this subject,[243] started and stopped Benemid on two occasions because he felt that it was responsible for substernal distress Eventually he suffered from recurring attacks of acute gout and was persuaded to resume Benemid together with colchicine He agreed to this regimen and since that time has responded in an excellent fashion He has suffered no further substernal distress or symptoms of coronary disease but is partially incapacitated by a right hemiplegia. The incidence of discontinuance was considerably higher in Gutman's series[106] Fourteen out of 120 patients stopped the drug after varying periods of time.

An active peptic ulcer is no contraindication to the anti-gout agents

J.N. was seen first in 1951 at the age of 53, having experienced acute attacks of gout since the age of 42 A duodenal ulcer was discovered in 1947 following a massive hemorrhage. The severity of his gout was responsible for his being placed on colchicine, 1 mg. a day, and Benemid, 2 Gm a day, in 1951 This dosage was continued for eighteen months He then suffered an attack of renal colic, and Benemid as well as colchicine was discontinued for one month A return of acute gouty arthritis prompted him to resume colchicine and Benemid An roentgenogram of his stomach revealed an active duodenal ulcer He was maintained on colchicine (1 mg 1 d) and Benemid (0 5 to 1 0 Gm 1.d) and has been on these drugs regularly through 1956, a total of more than five years. X-ray examinations have revealed an active duodenal ulcer, subsequently. The epigastric symptoms are controlled with an ulcer regimen, meanwhile, the gouty arthritis remains controlled on colchicine and Benemid.

J.N.'s clinical course is an example of the effectiveness of anti-gout agents coincident with an active duodenal ulcer which was present

several years before beginning daily ingestion of colchicine and Benemid

The administration of Benemid to patients with demonstrable renal impairment is a pertinent and practical problem Since a significant percentage of patients show evidence of renal dysfunction, these patients might be deprived of possible benefit if Benemid were found to be harmful Fortunately, untoward effects from Benemid have not been observed in our series or reported in the literature On the contrary, restoration of concentrating ability and increased excretion of P S P dye has been noted by Phillips[190] in one patient three years after beginning Benemid Our observations have been reassuring but not so spectacular Hence, we have proceeded with the colchicine-Benemid regimen, when indicated, irrespective of the severity of renal dysfunction and have not encountered any evidence to condemn such a practice

The prophylactic benefit from the colchicine-Benemid regimen may be evaluated in our series of patients at this time The experience of more than six years on the combined therapy is considered sufficient to justify definitive conclusions We are firmly convinced that, among currently available remedies, the combination provides the most effective treatment of any type of arthritis currently available Patients mildly or moderately afflicted lead normal lives in every major respect Patients with chronic deforming gouty arthritis continue to be handicapped in varying degrees but are not incapacitated There are several instances of patients, having retired prematurely or able to pursue a part-time job only, who, following the combined therapy, have resumed a full-time gainful occupation Not a single patient in our series has become permanently handicapped or crippled while on the regimen, not a single person has been forced to further restrict his gainful activities, and those who have complained of persistent joint pain due to chronic deforming gouty arthritis have been relieved of much of the interval distress Any handicap is mechanical from irreparable subcutaneous or osseous changes, and even this handicap shows some slow regression year by year It was stated four years ago[240] "It is not beyond the realm of possibility that resorption of urate deposits in periarticular and articular structures may be followed ultimately by restitution of function to the joints previously thought to be dam

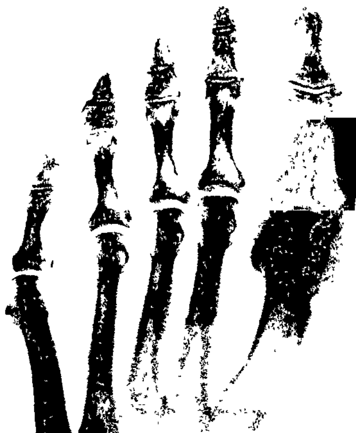


FIG 58 Roentgenogram of the left foot of a 58 year old male who is afflicted with severe tophaceous gout The history extended over a period of more than thirty years Extensive bony changes are present in the base of the proximal phalanx of the great toe and in the head and distal shaft of the first metatarsal Several osseous tophi have broken through the cortex into the soft tissues.

aged beyond help X-ray evidence is beginning to accumulate in the author's series which suggests that there may be resorption of osseous tophi and restoration of bony structures in patients who have taken Benemid 18 months or longer " Experience reveals that this hope was not in vain, since restoration of disordered joints has been observed subjectively as well as by x-ray



FIG 59 Roentgenogram of the same foot taken two years after FIGURE 58 The patient had been on colchicine and Benemid regularly Reconstitution of the bony structures, particularly along the distal shaft of the first metatarsal is noted.

The changes in the roentgenographic appearance of the left foot over a two-year period on patient E H are shown in FIGURES 58 AND 59 Extensive changes in the metatarsal-phalangeal joint are evident. Two years later, recalcification in selected areas was demonstrated in the x-ray films taken Similar findings are illustrated in the left foot of W M, another patient afflicted with chronic tophace-



FIG. 60. Roentgenogram of the left foot of a 42 year old male afflicted with extensive tophaceous gout.

ous gout. The films are shown before and after three years on the prophylactic regimen (FIGS 60 AND 61). The patient had been on 1 5 Gm of Benemid and 2.0 mg of colchicine during this period

The length of time that a patient should be on Benemid daily has not been determined It is our prediction that patients severely afflicted will be continued on Benemid indefinitely. Patients moderately afflicted probably may revert to smaller doses, meanwhile maintaining some colchicine daily as anti-articular prophylaxis Persons mildly afflicted have been taken off Benemid for varying periods of time after adherence to the regimen for two or three years These patients, however, have continued small doses of col-



FIG. 61 Roentgenogram of the same foot taken three years after that shown in FIGURE 60 Recalcification of the head of the proximal phalanx of the third toe is apparent

chicine regularly as noted above Although the combination with colchicine has produced excellent results, it cannot be called a cure in the case of the moderately or severely afflicted so long as a resumption of treatment remains as a possibility It is believed that most patients with gout should be on some colchicine regularly and probably should follow a course of combined therapy from time to time The following is an example

H C, first seen in 1950 at the age of 50, has been seen regularly in the intervening seven years There is a strong family history for gout Symptoms suggestive of a kidney stone preceded articular distress by five years The patient had undergone one severe attack and several minor attacks in the nine

months before he was seen first. Benemid was not available at that time but was prescribed later and 1.0 gm. taken daily for the three years (FIG 62). Because of a past history of "colitis", colchicine was not well tolerated, and he averaged from 2 0 to 6 0 mg per week of this preparation. At the end of three years of Benemid and four years of colchicine taken at relatively regular intervals, the patient became somewhat lax with his medication and a less rigid regimen was permitted In 1953 and thereafter, from four to six weeks might elapse without the ingestion of either anti-gout drug At other times several grams of Benemid and a maximum of 3 mg of colchicine

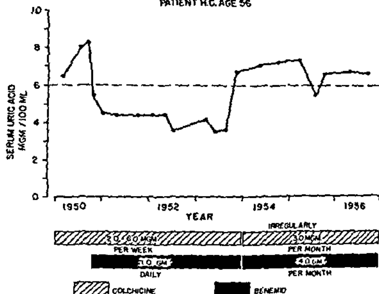


FIG 62 Experimental observations upon the serum uric acid concentration before, during and after daily Benemid intake.

might be taken each month Initially, during the colchicine Benemid regimen, there were five minor episodes of acute gout, each lasting a few hours only In the lower dosage period, the seizures were more frequent but not incapacitating in any instance. There have been no severe attacks, however, and no time lost from work during the seven-year period

This is an example of a patient who adhered strictly to a regimen of colchicine and Benemid regularly for several years The regimen

was liberalized considerably thereafter, with a slight increase in the acute attacks of arthritis but no increase in days lost from work

There are no other drugs required in the intercritical period if the combined regimen is followed Salicylates, cinchophen, the steroids and phenylbutazone have been recommended These agents will be discussed below under Acute Attack We have not prescribed for regular use by any patient any one of these preparations in the intercritical period It should *not* be forgotten that salicylates nullify the uricosuric action of Benemid

The dramatic results reported by Marson [165, 166] with salicylates justify careful scrutiny Patients given 6 Gm of sodium salicylate daily showed a more effective restoration of uric acid in the serum without disabling toxic symptoms than was obtained with an intake of 2 Gm of Benemid Also, the roentgenographic changes over a period of a few months with salicylates cannot be duplicated in our series with colchicine and Benemid prescribed over a much longer period Although nausea, tinnitus and deafness appeared at the onset of therapy with salicylates, the side effects disappeared in most patients thereafter Colchicine was used only for acute symptoms and was not prescribed daily, as is our practice Marson imposed no dietary or alcoholic restrictions but insisted upon a large intake of fluids These interesting reparative observations, it is hoped, will be confirmed

General measures during the intercritical period include attention to fluids, foodstuffs and exercise A high fluid intake is desirable Tap water should suffice in most instances Fluids with caloric supplements, such as milk or ginger ale, are adequate, but since gouty patients tend to gain weight, the additional caloric intake may be undesirable A patient with gout should develop the habit of drinking liberal quantities of tap water or alkaline water at mealtime as well as between meals The quantity consumed in the evening should be regulated to avoid nocturia Brochner-Mortensen [27] showed that the quantity of urate excreted increased as the urine volume increased, up to 1500 cc per day Augmenting the urine output beyond this quantity had little effect in increasing urate excretion or urate clearance Mugler and associates [178] observed that an increase in urine output from 0 5 ml /min to 5 ml enhanced the urate clearance from 7.0 ml /min to 14 ml /min Probably the

minimum urine output should approximate two liters per day. This amount necessitates an ingestion of fluids considerably greater than this volume Coffee, tea and cocoa need not be restricted They contain xanthine bases, which are not precursors of uric acid.[171]

There is meager evidence only that alcoholic beverages, consumed in moderation, aggravate the metabolic disturbance An occasional patient may produce satisfactory proof that a particular beverage acts as an inciting agent for an acute attack. The particular offender should be avoided if this correlation is confirmed On the other hand, most patients with gout are able to remain in a symptom-free state, meanwhile enjoying a temperate intake of alcohol if they so desire and if other anti-gout measures are respected It is believed that the harm from alcohol comes from the quantity consumed, rather than the quality Intemperance, as a general principle, is bad, as judged by current mores In the gouty patient it may be harmful physically as well The current generation of gout patients, in keeping with long-established traditions, appear to enjoy alcohol before or during meals A majority of patients appreciate the liberties provided, and the incidence of attacks is not increased A few patients sense a close association between consumption of a particular potion and the onset of acute joint symptoms Obviously, avoidance of the indicted drink is recommended I can recall only three patients with such a history. One believed that beer was an inciting agent, another red wine and yet a third, champagne Each patient, however, was able to enjoy and did enjoy, other types of alcoholic beverages with impunity.

Gouty diets are almost as numerous as students of the disease. Each kind of foodstuffs has been condemned and prohibited by some physicians, as well as praised and recommended by others More than a century ago, Gairdner[85] stated: "I have written to little purpose if it be not manifest to all that gout is not to be cured, not even benefited by a very low diet . . . I believe the most suitable regimen for the gouty is a mixture of animal and vegetable food, in which the former greatly predominates" The conclusions of Ewart[71] published in 1896 are of interest: "In gout more than elsewhere, because of its idiosyncracies, we should beware of dogmatism Gout is undoubtedly prevented by starvation; yet it does not follow that it may be cured on this plan Gout may also be

prevented by strict avoidance of animal food This does not prove that it need in every case be treated on vegetarian principles Again although gout may fail to attack some of those whose diet is exclusively animal, we are not warranted in prescribing meat as the diet for gout. Each case should be studied on its own merits." In the first edition of the "Principles and Practice of Medicine,"[18] Osler cautioned against the use of carbohydrates, and concluded "Meats of all kinds, except perhaps the coarser sorts such as pork and veal and salted ones, may be used Fats are easily digested and may be taken freely " It should be noted when this was written, rigid restriction of meat for gouty patients was the mode Marked differences of opinion exist today regarding the foodstuffs that should be permitted or condemned for gouty patients The current edition of an excellent textbook of medicine contains a full-page listing of the purine content of certain foods. Another popular textbook devotes five lines to the same subject It is little wonder that the practitioner tends to be confused Once a list of prohibited foods has been given to a patient, the tendency is to accept this with little question *Thou shalt not*, in regard to edibles, appears to be easier to follow than prohibitions in many other phases of human activity But progress may be reported, and there is better agreement, decade by decade, concerning the desirability of a balanced diet for patients with gout and of a liberalization of the protein content Although the author has taken an extremely liberal stand on the matter of proteins and alcohol, the recommendations in this regard are his and do not necessarily represent a consensus among contemporary rheumatologists

In 1938, the author's views[247] were stated and supporting evidence presented "We believe that the benefits of a low-protein and a scrupulously low-purine diet, however, have been exaggerated During a nine-month period in the hospital on a low-purine diet, one patient with moderately advanced gouty arthritis had 21 attacks of acute arthritis and spent 39 days in bed with severe gout In the 14 months after discharge he had seven acute attacks and spent only seven days in bed In this period at home, he had red meat at least once a day and enjoyed a moderate intake of beer and occasionally hard liquor In the hospital he was given no medication regularly except colchicine for acute symptoms. At home he took

colchicine for acute symptoms and, in addition, from 2 4 to 4 Gm of acetylsalicylic acid daily. At the end of the second period he began a third, which lasted 26 months. In this period he received, in addition to acetylsalicylic acid, 1.5 mg. of colchicine daily. During this time he had seven acute attacks of gout and spent eight days in bed . It is of interest that during the four-year period of observation the number of attacks per year and of days spent in bed during the low-purine regimen were about tenfold that observed while the patient was eating a liberal portion of meat each day."

In the current series, W.S. (PLATE XI) had a similar experience For more than one year this patient, upon his physician's advice, eliminated red meat completely from his diet and had small portions of fish or fowl not more than two days each week. During this period of time he had a number of attacks of acute gout and estimated that he was incapacitated one-fourth of the time He became so discouraged with the results that he returned to a protein diet and suffered somewhat less articular distress than he had formerly He was placed on colchicine and Benemid in 1950 and has not lost one day from his job during the subsequent six-year period. Meanwhile, he enjoys all kinds of meats, including game, supplemented by liberal quantities of alcoholic beverages

Studies during the past few years, utilizing isotope technics, have identified some of the precursors of uric acid and have removed some of the stigma from proteins Recent observations in the laboratory suggest that proteins may be no worse offenders as precursors of uric acid than are carbohydrates and fats. Some of the simpler biologic substances, as noted in the section on *Intermediary Metabolism*, such as carbon dioxide, formic acid, glycine, lactate and ammonia may contribute a nitrogen or a carbon atom to the uric acid molecule in the intermediary metabolism of this substance by the body The therapeutic implications regarding dietary restrictions for gouty patients are affected profoundly by these experimental data. It is apparent that carbohydrates as well as proteins and fats in the diet are potential precursors if carbon dioxide and formic acid contribute to the uric acid molecule in the human economy It is reasonable to assume, however, that some precursors may contribute to the uric acid molecule to a greater extent than others The best laboratory evidence in support of this

assumption has been furnished by Gutman's laboratory.[106] A mean decrease of 1.1 mg./100 ml. of serum uric acid was noted in a group comprising more than 100 gouty patients on a diet low in purines, poor in fats and containing not more than 70 Gm. of proteins daily derived exclusively from cereals, grain products, eggs, cheese, milk, non-leguminous vegetables and fruits. It was concluded that "The deterrent effect of restrictive diets on uric acid production in gouty patients was thus found to be of modest proportions." An intermediary view is expressed by Smyth:[236] "It is widely accepted that the diet of a patient with chronic gout should be low in purine-rich foods to relieve the already overburdened mechanism for the disposition of purines. There is no convincing evidence to prove that adherence to a rigorous purine-free diet reduces the frequency of acute attacks or prevents chronic arthritis or complications of gout."

The potential harm from a liberal intake of protein daily has been emphasized unduly and not supported by clinical experience or laboratory experiments. It should be appreciated that proteins and certain nucleoproteins yielding pyrimidine bases form urea as the nitrogenous end-product, and not uric acid. We have never recommended a low-protein or a scrupulously low intake of purine substances in the treatment of our patients except for those with a sufficient degree of renal insufficiency to have resulted in azotemia. The added load imposed by an average protein intake has been respected in well-developed renal insufficiency. A gouty patient, in exceptional instances, will note a close association between the intake of a particular protein and an acute attack of gout. Avoidance of the offender is advised if this sequence of events is repeated. A diet balanced in content of fat, protein and carbohydrates is recommended in the absence of suggested data. Those foodstuffs high in content of purine substances should be avoided at all times, but this restriction usually imposes no hardship upon the patient even though he may be a gourmet. Meat extracts, sweetbreads, anchovies, liver, kidney, spleen and tongue are the only items under suspicion.

The caloric content is believed to be as important as the specific items. A few gouty patients tend to be overweight. This imposes a burden upon the cardiovascular system as well as upon the weight-bearing joints. Obesity, as a general principle, is thought to be

undesirable for the healthy as well as for those suffering from a chronic disease. In a review of our own gouty patients we must admit the number encountering serious trouble prematurely because of obesity is so small as to be negligible. The general rules for maintaining a normal body weight are believed to apply.[154]

Other phases of normal living may be pursued without compromise. Patients who enjoy out-of-door activities should be permitted to continue them, contingent upon general rather than specific rules Golf, tennis, shooting or whatever activity appeals to the individual should be permitted Nay, they should be encouraged if pursued with proper respect for the regimen of medication Sydenham[239] believed that exercise had certain preventive properties "Now these [formation of tophi] may be guarded against, whereby we obtain the due diffusion over the whole body of the humours that generate gout, instead of their accumulation in any particular part of it by preference I have found in my own person that long and daily exercise not only stops the generation of chalkstones, but even dissolves old and hard ones already formed, provided only that they have not gone so far as to have converted the outer skin into their own proper substances"

The need for awareness of an impending attack is not so critical as formerly but should not be ignored. Polyuria, gastrointestinal unrest, suppression of sweating and a gain in body weight may portend the development of acute symptoms. A fall in barometric pressure may accompany some or each of these symptoms in patients with rheumatoid arthritis[248] At the first perception of prodromata and before the appearance of joint distress, the ingestion of additional colchicine (one or two tablets) may be desirable An extended course of colchicine is unnecessary if the attack does not materialize within a few hours Colchicine should be continued until an adequate amount has been taken if joint symptoms progress and a full-blown attack *seems imminent It is expedient for the* patient to understand the vagaries of the prodromata and to anticipate the full development of an acute attack The patient should be instructed to proceed without immediate professional advice, since a few hours' delay in beginning the ingestion of colchicine may influence the severity as well as the duration of an acute episode

Acute Attack

If proper deference is paid to the prophylactic regimen, attacks of acute gout should be infrequent in incidence and, if the malady is recognized early in its natural history, mild in severity The undiagnosed case of gouty arthritis or the poorly or untreated acute attack comprises the significant distress group in the acute category The most valuable drug in the treatment of the acute attack of gout continues to be colchicine This may be combined with phenylbutazone or ACTH, but it has not been replaced by either agent The use of colchicine alone will be discussed initially, since the drug selected in the unconfirmed case may carry diagnostic implications as well as therapeutic value "Of all the *specific remedies* which have been vaunted as cures for gout, colchicum alone claims notice There can be no doubt that this drug really has a specific power over the disease and that it not only relieves the pain and inflammation which accompany an acute attack in a joint, but it also removes the symptoms of the disease in other parts of the body "[85]

The amount of colchicine prescribed should be based upon the severity of symptoms The subsidence of distress in a mild attack may follow the ingestion of not more than four or five single doses of colchicine 0 5 mg (1/120 grain). A moderate or a severe attack requires the "full course " This is achieved only by the periodic ingestion of colchicine until the onset of gastrointestinal distress If the attack has ominous characteristics from the onset, the "full course" may be achieved by the ingestion of two colchicine tablets every two hours or one tablet every hour until the anticipated side effects appear It is important for the patient to evaluate, if possible, the severity of the attack at the onset of symptoms The mild attack will be suppressed with a few colchicine tablets if treatment is started early, while the severe bout will be adequately and promptly managed only through a full course of colchicine

The mild attack may be handled without interruption of daily routine, and probably without medical advice if the patient has been properly instructed Each patient, in order to be adequately indoctrinated, should proceed with a full course of colchicine, once the presumptive diagnosis has been entertained during the first

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acute attack under observation. A deficiency may be revealed later if the patient has not received such indoctrination The usual number of colchicine tablets required to produce gastrointestinal distress varies between ten and fourteen, taken over a span of the same number of hours There is no satisfactory explanation for the obligatory induction of gastrointestinal symptoms in order to achieve a full therapeutic effect; the empiric observation is well substantiated, however There is general agreement that the full therapeutic action of colchicine is accomplished in the severe attack only if unmistakable gastrointestinal distress develops Patients who attempt to circumvent this distress by the ingestion of smaller quantities of colchicine or who take colchicine over longer periods of time receive submaximal benefit. Satisfactory subsidence of symptoms may be expected if the ingestion of colchicine is begun at the onset of acute symptoms and a full course pursued Usually the joint or joints involved begin to quiet down near the close of the colchicine schedule, and hour by hour thereafter, they become progressively less painful Significant improvement should be expected within 24 hours after the beginning of colchicine ingestion, at which time the patient is convinced that he is well on his way to recovery Within 24 hours after the conclusion of the full course of colchicine, the acute distress should be dissipated and significant return of function of the affected joints apparent

A full course of colchicine may be ineffective because of one of several reasons (1) Prompt institution of the colchicine regimen did not occur The desired effect may not be achieved promptly if acute symptoms are permitted to persist for one or more days before beginning colchicine (2) The course of colchicine may have been interrupted This is an error that patients sometimes commit If ten doses have been found by experience to be necessary for suppression of joint symptoms, the ingestion of five doses on the first day and five doses on the following day leaves much to be desired clinically, although mathematically this would appear to be sufficient. Gastrointestinal symptoms may develop on the second day without adequate symptomatic relief Once colchicine is started, it should be continued without interruption at hourly or two-hourly intervals as noted above If articular symptoms develop in the evening or during the night, ingestion of colchicine should not be inter-

rupted It is more important in the treatment of the acute attack that the patient receive colchicine regularly than that he receive a continuous night's rest A sedative such as a barbiturate may be given to enable the patient to return to sleep after each dose of colchicine if restlessness persists (3) There may be some complicating factor which precipitated the acute attack and which persists as the inciting agent

The failure to appreciate the proper method for administering colchicine has been partially responsible for its unenthusiastic recommendation by some physicians and use by their patients The apparent inevitability of gastrointestinal distress has contributed to its unpopularity Gastrointestinal disturbance is unpleasant, but in our experience this side effect does not constitute a contraindication A preliminary cathartic or a purgative is frowned upon since it may be impossible to determine whether purgation has followed such a drug or is the indication for cessation of colchicine

At the onset of nausea, vomiting or diarrhea, ingestion of colchicine is to be stopped, irrespective of subsidence of joint symptoms, and a gastric sedative ordered Tincture of camphorated opium, 5 ml, is recommended, with the dose repeated every two or three hours as needed The administration of a gastrointestinal sedative, a significant aspect of proper indoctrination in the treatment of the acute episode, is as desirable at this stage of therapy as the institution of a full course of colchicine at the onset of articular distress Every effort should be made to rehabilitate the patient as rapidly as possible with respect to affected joints as well as with respect to the altered gastrointestinal functions Because of the irritative action of colchicine upon the gastrointestinal mucosa, it is undesirable to repeat a full course, should a second course be indicated, or to resume the prophylactic ingestion of colchicine until after a lapse of 48 hours following the termination of a full course In our experience, if treatment is begun early, less than five per cent of severe attacks fail to respond to the first full course and either require a second course of colchicine or require some other anti-gout agent

Colchicine was introduced early in this discussion because of the emphasis that should be placed upon it It should be the first drug to be considered in the treatment of the acute attack Never-

theless, several other preparations are now available as an adjunct to colchicine, or in some instances as a substitute Each has merit, each has strong proponents in support of its use, but a proper perspective regarding the value of the several adjuvants is lacking In planning for a possible subsequent recurrence of acute symptoms, efforts should be directed to include only those items in the "must" category that are feasible for the patient independent of immediate medical advice. This restriction excludes, as a recommendation for a routine procedure, any intravenous or parenteral preparation. If acute symptoms begin at two o'clock in the morning while the patient is at home in bed, he should be familiar with the proper recommendations and be prepared to carry them out without delay. The expenditure of unnecessary efforts and the inevitable delay in beginning treatment follow either the preparation and visit to the hospital or the night call of the physician to the home. The indications for parenteral preparations will be discussed after a consideration of phenylbutazone.

Phenylbutazone is an effective anti-inflammatory and analgesic drug. It is not specific for acute gout but valuable, nevertheless Some physicians recommend it as the sole drug in the treatment of the acute attack, others recommend it in conjunction with colchicine. We use it only in conjunction with colchicine There are several circumstances in which phenylbutazone may be helpful. (1) If the patient has been on the colchicine-Benemid prophylactic regimen for a relatively short period of time, the full effect of these agents will not have become manifest, and acute attacks continue to be a serious problem In this circumstance, less than a full course of colchicine is prescribed (2–3 mg) together with 800 mg. of phenylbutazone during the initial 12 hours Phenylbutazone (800–1200 mg) is continued for 24 or 36 hours after the termination of the colchicine ingestion This modification may avoid the undesirable gastrointestinal distress and expedite rehabilitation. (2) An inadequately or poorly treated attack of gout that has not responded to a full course of colchicine may benefit from supplementary phenylbutazone. (3) Low-grade symptoms may persist for some unexplained reason after the full course of colchicine Rather than resort to a second course of colchicine, from 400–600 mg of phenylbutazone may be given for two or three days [142]

Kuzell is one of the more enthusiastic advocates of phenylbutazone This drug was evaluated by him in several hundred patients with acute or chronic gouty arthritis[143] Males responded more favorably than did females, and acute gout was found to be more amenable to phenylbutazone than was chronic gouty arthritis Ninety-three per cent of the patients were completely relieved or showed major improvement in 48 hours, while 84 per cent of the total acutely and chronically affected responded within this period of time These results are similar to those that may be expected with a full course of colchicine

Wilson and associates[268] have recommended somewhat larger doses On the first day 400–800 mg of phenylbutazone are given orally at a single dose with 200 mg two hours and again four hours later Thereafter, 300–400 mg are given daily until all signs of joint inflammation have disappeared Continuation of therapy beyond four days usually was not necessary These investigations emphasize the importance of serum phenylbutazone levels of 3 mg /100 ml or higher in attaining relief of pain

The toxic effects are not serious in the management of the acute attack save for hypersensitivity Even the staunchest advocates advise caution in the long-term use of phenylbutazone, because of its toxicity Untoward effects include edema, nausea, epigastric distress, skin rash, vertigo, visual disturbance, lethargy, nervousness, hypertension, stomatitis, hepatitis, anemia, leukopenia and purpura[100] Nineteen per cent of the patients in one series[269] showed clinical toxicity which was not serious enough to warrant discontinuation of the medication, while 7 per cent were forced to discontinue the drug Johnson and associates[131] observed serious toxic effects in nine of sixteen patients with chronic gouty arthritis Evidence of toxicity occurred as late as the fourth month of therapy in one instance Smyth[230] has reported the long-term use of phenylbutazone in four patients with chronic gout Undoubtedly, other physicians are evaluating the use of phenylbutazone in the intercritical period In the absence of additional evidence or of reports of experience, we believe in limiting phenylbutazone to cases resistant to other established forms of anti-gout treatment

Intravenous colchicine, as an adjuvant to the oral preparation, has enjoyed limited popularity in the treatment of the acute attack

and is entitled to a restricted but definite place in the armamentarium [241] Graham has stated clearly the indications for this route [97] Intravenous colchicine should be used to complement, but not to supplement, the oral route. Patients should not be dependent upon an intravenous medication at frequent intervals if the oral preparation will suffice There are some patients with an irritable gastrointestinal tract who tolerate oral colchicine poorly and who profit from the intravenous preparation The preferred dose, when indicated, is one-half of the full course orally and the remainder intravenously *Two to three injections are required if the intravenous* route is chosen exclusively, and approximately two-thirds of the estimated oral dose is administered Either regimen avoids gastrointestinal disturbance Three ampules (0 5 mg each) are administered at each injection, which is repeated every three hours for a second or a third dose Davis and Bartfeld [62] reported beginning alleviation of distress shortly following the first injection. A total *of sixteen attacks were investigated by them with favorable results*

Adrenocorticotropin and the adrenal steroids are of restricted value in the treatment of acute gouty arthritis The newest adrenal steroids, prednisone and prednisolone, are less effective in the management of the acute attack than is ACTH, and if any agents in this category are employed, the latter is preferred. There are a number of satisfactory reports of the use of ACTH in the acute *attack Gutman [105] noted complete remission in 60 per cent of the* patients within 24 to 48 hours The response was unsatisfactory in 20 per cent The other patients either had a good initial response, followed by a relapse, or had a delayed response with a complete remission not appearing for several days Our results are similar to those of Gutman Others have been more enthusiastic. Margolies and Caplan [163] reported one patient who recovered from the acute attack within 75 minutes after the administration of 50 mg of ACTH In another instance, the patient was able to walk and bear weight with comfort within an hour With the availability of ACTH-gel or other long-acting adrenocorticotropins, from 40 to 80 units are given intramuscularly at a single injection as an *adjuvant* to a modified course of oral colchicine. Another reason for combining colchicine and ACTH is to avoid a relapse, a possibility when ACTH is used exclusively [270]

There are several other drugs that have been recommended in the treatment of the acute attack. Salicylates and cinchophen have enjoyed wide popularity in the past, but neither one is specific nor so effective as colchicine. Cinchophen should not be considered as a specific for gouty arthritis and should not be used in the treatment of this malady. Because of the similarity in the names, colchicine and cinchophen, some physicians have confused them and even hesitated to use colchicine, apparently associating it erroneously in their minds with the toxicity of cinchophen. Salicylates are less toxic but are not specific for gout and have not been recommended routinely in this clinic. Codeine in small quantities, 30 or 60 mg., is indicated in selective instances but should not be prescribed regularly. The use of codeine or any other hypnotic drug during the acute attack is unusual for the patients in our series. Intravenous heparin has been accredited with anti-gout properties. Another anticoagulant, biscoumarin acetate,[232] has been studied for its uricosuric properties but has little or no analgesic action. Obviously, drugs with an anticoagulant property have no place in the current therapy of acute gout. Colcemide or demecolcine (desacetyl methylcolchicine), a chemical relative of colchicine, has been used clinically in the treatment of the acute attack. This substance is assumed to be less toxic than colchicine, as determined by animal experiments. When the preparation was used intravenously 75 per cent of the patients enjoyed a complete remission within 48 hours after the administration of from 1 to 4 mg.[141] Diarrhea occurred in two of twenty patients. The oral preparation in ten patients caused no gastrointestinal trouble. From 5 to 8 mg. of the drug resulted in improvement after a similar period of time as the intravenous preparation. The toxicity has not been determined save for the development of alopecia totalis, as reported by Mikkelsen and associates.[177] I have used this preparation in the treatment of a limited number of acute attacks and believe that judgment should be reserved at the present time regarding its value.

An effusion of appreciable size may develop if acute gout settles in the knee. Removal of excess fluid is desirable when the effusion interferes with flexion of the knee and locomotion. There should be no hesitation in removing the excess fluid. A single aspiration is sufficient in most instances. An elastic bandage should be

applied and worn for 24 hours following the removal of fluid. The time required for the recovery of the affected joint may be prolonged unnecessarily if aspiration is not accomplished Aspiration of an acute joint does not eliminate the need for full doses of colchicine.

T D, a 42 year old male when seen in 1946, had had his first attack of acute gout at the age of 26 The correct diagnosis was not made until several years later The attacks were induced on several occasions by emotional upsets and, on one occasion, by parenteral administration of vitamin B_1 He suffered as many as six attacks per year and was off the job for as long as three weeks with one of the episodes. The concentration of uric acid in the serum ranged from 8 to 10 mg/100 ml The patient was lax in following recommendations, he did not report to the clinic and continued to have several days of incapacity each year between 1950 and 1956. He was admitted to the hospital in 1956 with an acute effusion of the right knee following an automobile accident A full course of colchicine, which was taken before coming to the hospital, had failed to relieve the effusion although articular distress was less Aspiration was carried out, and more than 80 cc. of viscous yellow fluid was removed Rapid recovery followed thereafter.

General measures for the treatment of the acute attack include a light diet, an abundance of fluids and rest of the affected joints Since a severe attack may be associated with a significant increase in body temperature and an increased loss of sensible perspiration, an augmented fluid intake serves a dual purpose. Replacement of fluid lost by way of the sweat glands is imperative. Equally important is the need for an adequate quantity of fluid for renal transport of uric acid in order to minimize the tendency for the precipitation of urates in the tubules Augmented fluids may be accomplished by including in the diet, broth, soup, fruit juice or milk, fluids which contain minerals as well as calories

No useful purpose is served if severely affected joints are kept active or subject to weight-bearing so long as acute symptoms persist. When not more than one or two joints of the upper extremities are involved, the application of an arm sling may permit continued ambulation. Restriction to a chair or bed is imperative if one or more joints of the lower extremities are severely involved A cradle for the bed covers is desirable as soon as the patient takes to his bed. Local application of moist dressings, dry heat or cold compresses, respectively, have been recommended by some phy-

icians The value of each of these procedures is uncertain Professional physiotherapy is not indicated if the acute episode has been managed properly. However, a poorly treated attack which persists for several weeks may be associated with local muscle atrophy and poor joint function following relief of acute articular symptoms, and physiotherapy is indicated in such a situation Slippers should be worn during early ambulatory convalescence only, and as soon as street shoes are comfortable they should replace slippers

Surgical Treatment of Chronic Deforming Gouty Arthritis

The surgical treatment of advanced tophaceous gout has much to commend it and may rehabilitate a partially incapacitated individual. Duckworth [67] in 1889 noted "Any surgical interference with joints affected with concretions or with late arthritis changes has always been regarded with disfavor It must be admitted that many surgical questions which have been considered closed need to be reopened and to be looked at again from the altered standpoint of antiseptic surgery Gout will probably not form an exception to this" Several years ago at the Massachusetts General Hospital in Boston, Dr R R Linton reopened the question of surgical interference in chronic tophaceous gout with excellent results [151] At the Buffalo General Hospital in recent years similar good results have been obtained by Dr Peter Casagrande of the Orthopedic Service tman [106] has not found it necessary to resort to surgery but relies upon the medical treatment for resolution of large tophi We approve of the more rapid correction, meanwhile beginning the use of colchicine and Benemid

Large subcutaneous tophi which have become unsightly are removed, as well as smaller tophi of the hands and feet which interfere with the wearing of gloves and shoes Tophi in exposed areas of the body, such as about the olecranon process, the patella and the heels, are unsightly as well as potential sites for sinus formation Tendon involvement by tophi which interfere with motion or locomotion also are removed It is important in removing a tophus from the subcutaneous tissues to practice extensive curettage of the urate deposits The quantity of urate that may be removed at times is surprising The failure by some surgeons in the past to obtain a good postoperative result is believed to be related partially to the failure

to remove adequately the urates in the operative field. Formerly, functionless digits were amputated (FIG 63), but with the availability of a powerful uricosuric agent, this procedure is no longer necessary



FIG 63 Roentgenogram of the right foot of the patient described in FIGS 57 and 58. The phalanges of the great toe were amputated because of osseous and subcutaneous tophi. The first metatarsal head has not been the site of visible tophi

The surgical treatment of a discharging urate sinus involves little or no risk from postoperative infection Even before the antibiotic era the incidence of postoperative infection was negligible It is important to remember that parenteral penicillin is contraindicated because of the possible induction of an acute attack of arthritis; a broad spectrum antibiotic is preferred. Most helpful in the medical handling of a gouty patient undergoing surgery is the preoperative administration of 1.5 mg. of colchicine daily, if the patient is not already on rations of this magnitude Patients should receive colchicine for at least three days prior to surgery in order

to minimize the tendency for the development of postoperative gouty arthritis It was the experience of Linton and Talbott [131] that the incidence of postoperative gouty arthritis was reduced from more than 80 per cent to eight per cent Intravenous colchicine may be used in the postoperative period Should the reader desire technical information regarding the specific surgical procedures the original article should be consulted

EPILOGUE

"THAT THE SIZE OF THE BOOK *is little, is owing to the cure For 'tis not much to purpose, to trouble the publick with copious theorys, long cases, and pompous nicetys upon a disease; if we can but cure it I have indulg'd myself no further liberty in speculation, than might be useful to discover the nature of the distemper; whereby we may better treat our selves in a fitt and out of a fitt, better known how to prevent or protract its returns, or moderate them when they come*" Stukeley, 1734[238]

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INDEX

Achilles, 3
Acid
  aspartic, 30
  benzoic, 50
  inosinic, 30
ACTH (adrenocorticotropic hormone), 34, 59, 126, 129, 147, 178
Acute gout, 173
  clinical description, 95, 97
  diagnosis, 125
  duration of attack, 175
  fever, 97
  frequency of attacks, 100
  frequency of joint involvement, 100
  interval between attacks, 100
    (*see also* Intercritical gout)
  joint changes, 100
  leukocytosis, 98
  pain, 96
  pathogenesis, 61, 67
  precipitating factors, 107
  premonitory symptoms, 100, 174
  prevention, 145
  sedimentation rate of blood, 98, 120
  symptoms, 97
  systemic reactions, 97
  treatment, 173
Adenine, 31, 50
Adrenal cortex, 28
Aetius, 2
Age, 19, 40, 134, 152
Agglutination, sheep erythrocyte, 68
Agrippa, 3
Albuminuria, 15, 109, 124, 144
Alcohol, 16, 23, 169
Alexander the Great, 3
Alexander of Tralles, 2
Allantoin, 23, 29
Amyloid, 66, 144
Anemia
  erythronoclastic, 121
  hemolytic, 118
  juvenile poikilocytic, 121
  pernicious, 118
d'Angelo, Matthew, 3
Animals, lower, 17, 23, 30
Ankylosis, 63, 70, 134
Anne, Queen, 3
Antibiotics, 142
Aretaeus the Cappodocian, 2
Argentina, 21
Arteriosclerosis, 113
Arthritis
  acute gouty, 173
  chronic gouty, 103
  differential diagnosis, 129
  gonorrheal, 142
  incidence, 17
  infectious, 17, 142
  osteo, 62, 147
  progenic, 142
  rheumatoid, 41, 63, 137, 139, 147
Associated diseases, 116
  Cooley's anemia, 118
  diabetes mellitus, 116
  erythronoclastic anemia, 121
  essential lipemia, 116
  hemolytic anemia, 118
  hemophilia, 121
  hypercholesterolemia, 116
  juvenile poikilocytic anemia, 121
  lead intoxication, 116
  leukemia, 116, 119
  lymphoblastoma, 118
  myelofibrosis (myelosclerosis), 116, 120
  multiple myeloma, 116, 121
  non tropical sprue, 121
  obesity, 116
  pernicious anemia, 118
  polycythemia vera, 116, 117
  purpura, 121
Atticus, 3

Bacon, Francis, 3
Bellerophon, 3
Benemid (*see* Probenecid)
Bird, 17, 27, 37

Blastomycosis, 142
Bocking, Ralph (Radulphus), 3
Boerhaave, 3
Butazolidin (*see* Phenylbutazone)

Caelius, Aurelianus, 2
Calcium deposits, 63, 73
Calcium, gout, 71
Calculus (*see* Lithiasis)
Calvin, John, 3
Carbon, 13
Carboxamid, 30
Carinamide, 50
Catalase, 23
Charles the Great, 3
Charles II, 4
Chatham, 3
Chesterfield, Lord, 3
Chicken, 17
Chinese, 21
Chronic gout
  clinical description, 103
  complications, 107
  diagnosis, 122
  pathology, 60
  prognosis, 142
  surgical treatment, 181
  treatment, 146
  x-ray changes, 69
Cinchophen, 126, 152, 167, 179
Clinical description, 95
  acute gout, 95, 97
  chronic gout, 103
  intercritical gout, 100, 101
Codeine, 179
Colcemide, 147, 179
Colchicine, 48
  carcinogenic action, 49
  diagnostic value, 126
  dosage, 149
  full course, 126, 151
  intravenous, 177
  pharmacologic action, 126
  preoperative use, 182
  prophylaxis, 51, 147, 149
  structure, 48
  tolerance, 151
  toxicity, 49
  use in acute gout, 126, 147
Colchicum, 1, 4, 48, 147, 149
  autumnale, 4
Complications, 107
  arteriosclerosis, 113
  hypertension, 113
  lithiasis, 110
  ocular, 115
  renal, 107
  thrombophlebitis, 114
Condé, 4
Congreve, William, 3
Cooley's anemia, 118
Corneli, George, 3
Coronary artery disease, 66, 113
Cortisone, 126, 147
Cromwell, 3
Cruickshank, 4
Cytochrome oxidase, 23
Cryoglobulinemia, 121

Dalmatian coach hound, 42
Darwin, Charles, 4
Definition, 5
  acute gouty arthritis, 6
  chronic deforming gouty arthritis, 6
  gout, 5
  gouty diathesis, 6
  intercritical period, 6
Demetrios, 3
Dessicans, osteochondritis, 71
Desquamation, 99
Diabetes mellitus, 116
Diagnosis, 122
  acute gout, 125
  albuminuria, 124
  ancillary items, 123
  clinical description, 125
  colchicine response, 126, 129
  critical criteria, 125
  differential, 122, 129
    acute cellulitis, 97, 142

Diagnosis—*Cont'd*
acute rheumatic fever, 129
osteoarthritis, 139
rheumatoid arthritis, 134
family history, 123
hypertension, 124
lithiasis, 123
post attack criteria, 127
serum urate concentration, 124, 125
tophi, 125, 127
x ray findings, 128, 142
Diathesis, gouty, 6
Diet, 16, 23, 35, 104, 146
acute gout, 180
prophylactic period, 168
Differential diagnosis, 129
Dog, 17
Dosage (*see* Treatment)
Dysplasia, fibrocystic, 142
Dryden, 3
Duration of attack of acute arthritis, 99

Eau médicinale, 4
Ebers papyrus, 1
Effusion, joint, 179
Egyptian archeology, 1
Enchondromata, 142
Endocrine disorder, 27
England, 21
Enzymes, 23
Erythronoclastic anemia, 121
Etiology, 22
allergy, 27
constitutional inferiority of kidneys, 24
destruction of urates, 23
diet, 23
diminished excretion of urates, 23
endocrine, 27
heredity, 27
increased formation of urates, 23
lead intoxication, 23
purine metabolism, 26
renal, 24
Europe, 21
Exercise, 167, 172

Family history, 8, 123
Females, gout, 11, 19, 27, 39
Fever, 20, 97
rheumatic, acute, 20, 96, 134
Fielding, 4
Filipino, 21
Fluid intake, 153, 158, 167
acute gouty arthritis, 180
intercritical gout, 153, 158, 167
Formate, 30
Francois III, 4
Franklin, Benjamin, 3, 110

Galen, 2, 8
Gene, 11, 14
Geneology, 9, 12
Germany, 21
Gibbon, 4
Gilbert and Sullivan, 4
Gillray, 4
Globulin, gamma, 68
Glomerular filtrate, 25, 42, 58
Glomerulonephritis, 16, 100, 120, 144
Glutamine, 30
Glycine, 51, 170
Goethe, 4
Gray, Thomas, 3
Group, blood, 11
Guanine, 31

Hallus valgus, 87
Hamilton, 4
Harvey, William, 3
Heberden, William, 110
Hemophilia, 121
Henry VII, 3
Henry VIII, 3
Heredity, 7, 19
Hieron, 1
Hippocrates, 1, 27
Historical, 1
Homozygote, 11

Horse, 17
Howe, Lord, 3
Hunter, John, 4
Husson, Nicholas, 4
Hypercholesterolemia, 116
Hypertension, 124, 144
Hyperuricemia, 126, 137, 139, 145
  gouty arthritis, 126
  idiopathic, 41
  non affected relatives, 10, 145
Hypoxanthine, 30

Incidence, 17
  age, 13, 19
  nationality, 21
  race, 21
  season, 22
  sex, 19
  social status, 21
India, 21
Intercritical gout, 6, 100
Intermediary metabolism, 28
  diet, 35
  glycine incorporation, 30
  isotope, 29
  metabolic pool (miscible pool), 32
  precursor, 29
  turnover rate, 32
Isotopes
  metabolic pool (miscible pool), 32
  C^{13}, 31
  N^{14}, 32
  N^{15}, 24, 26, 31
  precursors of uric acid, 29
  turnover rate, 32
  use in investigation, etiology, 24

Johnson, Samuel, 4

Kidney, 107
  amyloid deposits, 66, 144
  differential excretion of urate, 24
  glomerulonephritis, 16, 109, 126
  infection, 66
  pyelonephritis, 66, 126
  vascular nephritis, 66, 144

Lactoperoxidase, 23
Landor, 4
Laville's tincture, 4
Lead intoxication, 23, 40, 116, 126
Leprosy, 142
Leukemia, 40, 116, 119
Linnaeus, 4
Lithiasis
  calcium, 9, 15, 113, 124
  urate, 1, 55, 110, 123, 158
Lorraine, Dukes of, 4
Louis XIV, 4
Lowell, James R., 3
Lucian, 2
Luther, Martin, 3
Lymphoblastoma, 118, 126

Menstruation, 11, 19, 27
Milton, John, 3
Morgagni Stewart Morel syndrome, 117
Multiple myeloma, 50, 116, 121
Murexide test, 5
Myelofibrosis (myelosclerosis), 40, 116, 120

Nationality, 21
Negro, 21
Nephritis
  glomerular, 16, 109
  pyelonephritis, 66, 126, 144
  vascular, 66
Neurofibromatosis, 142
Newton, 4
$Nitrogen^{14}$, 32
$Nitrogen^{15}$, 24, 26, 31
Node, Heberden, 139, 142
Nodule, rheumatic, 134

Obesity, 116
Oedipus, 3
Osteoarthritis, 62, 139
Osteogenesis imperfecta, 117

Paget's disease, 114, 117

Pain, 96
Pannus, 63
Paré, Ambrose, 4
Pathogenesis of symptoms, 61, 67
Pathology, 60
  articular structures, 60
  kidney, 61, 65
Paul of Aegina, 2
Penicillin, 50, 97, 182
Pharmacology of anti gout drugs, 48
Phenosulfonphthalein, 25, 53, 144, 161
Phenylbutazone (Butazolidin), 56, 126, 147, 167
  clinical benefit, 56, 127, 176
  toxicity, 57, 177
4 (phenylthioethyl) 1, 2 Diphenyl 3 5 Pyrazolidinedone, 58
Philoctetes, 3
Phosphoriboxylamine, 30
Pigeon, 11
Pitts, the William, 3
Plesthenes, 3
Podagra, 5
Polycythemia vera, 27, 40, 116, 118
Polysaccharides, serum, 68
Pool, metabolic (miscible), 32, 54, 145
Portland powder, 4
Postoperative gout, 182
Precipitating factors, 103
  alcohol, 103
  drugs, 105
  food, 104
  infection, 106
  operation, 104
  sex, 104
  trauma, 104
Precursors of uric acid, 29
Premonitory symptoms, 100, 174
Prevention, 145
Priam, 3
Probenecid (Benemid), 25, 34, 50, 126, 149
  clinical benefit, 52
  continuous use, 152
  dose, 153
  prophylaxis, 51, 149
  toxicity, 54, 153, 158
Prognosis, 142
  uremia, 143
Prophylaxis, 6, 150
Protesilaus, 3
Pseudo hyperparathyroidism, 147
Purine metabolism, 30
Purpura, 121
Pyelonephritis, 66, 126, 144

Race, 21
Radulphus (Ralph Bocking), 3
Relatives, nonaffected, 10, 145
Renal exchange, 42
  effect of drugs, 43
  urates, 25
Renal impairment (see Kidney)
Reptile, 17, 27, 29, 37
Reynold's specific, 4
Rheumatic fever, acute, 129, 134
Ribotide, glycine amide, 30

St Richard of Wyche, 3
Salicylates, 34, 48 59, 126, 129, 152 167, 179
Saxe Marshall, 4
Scripture, 1
Season, 22
Sedative, gastric, 175
Sedimentation rate of blood 98 129
Seneca, 2, 8
Serum urate (see Urate concentration serum)
17 Ketosteroid excretion, 27
Sex, 19, 129
Smith, Sidney, 3
Social status, 21
South America, 21
Sprue, nontropical, 121
Steroids, adrenal, 34, 59, 127, 167 178
Substances, purine, 5
Sulfonamide, 55
Surgical treatment, 181
Sydenham, 4

Symptoms
acute gout, 97
chronic gout, 103
intercritical gout, 6, 101

Thread test, 5
Thrombophlebitis, 114
Titer, fibrinolysin, 68
Tophus, 5, 17, 70, 95, 125, 127, 134, 142
distribution, 127
formation, 61
resorption, 156, 162
urate content, 5
Treatment, 146
acute attacks, 173
ACTH (adrenocorticotropic hormone), 173, 178
adrenal steroids, 178
cinchophen, 179
colchicine, 173, 177
exercise, 180
diet, 180
fluid intake, 180
phenylbutazone, 173, 176
probenecid (Benemid), 153
salicylates, 179
intercritical period, 148
alcohol, 168
colchicine, 149
diet, 155, 168
fluids, 153, 158, 167
probenecid (Benemid), 149
proteins, 155, 169
purine substances, 155, 169
postoperative gout, 182
surgical, 157, 181
Tuberculosis, 20
Turkey, 17
Turnover rate, 32
Tyrannion, 3

Ulysses, 3
Urate calculus (*see* Lithiasis)
Urate clearance, 25, 43
Urate concentration
body fluids, 5, 34, 37
method of measuring, 38
serum, 5, 10, 36, 38, 123, 125, 129, 134
sex difference, 39
spinal fluid, 40
synovial fluid, 40
urine, 44
whole blood, 38
Urate deposits
cartilage, 60, 63, 66
epiphyseal bone, 70
heart, 61
kidney, 65
subcutaneous tissue, 61
Urate exchange, 26, 42
Urate excretion, 35
ACTH (adrenocorticotropic hormone), 28, 34
caronamide, 50
cinchophen, 45
colchicine, 49
Diodrast, 25, 45
ethyl biscoumacetate, 47
glucose, 46
phenylbutazone (Butazolidin), 43
47, 56
4 (phenylthioethyl) 1, 2 Diphen
3, 5-Pyrazolidinedone, 58
probenecid (Benemid), 34, 43, 4
52, 154
salicylate, 34, 38, 43, 45, 59
Urate Tm, 43
Urea, 26, 29, 37
Uremia, 66, 143
Uric acid (*see* Urate)
Uricase, 23
Uricosuric agents, 34, 125, 152
Urine
albumin, 15, 109, 124, 144
urate concentration, 44
Uruguay, 21

Vertoperoxidase, 23

Vessels, coronary, 66, 113
Villehardouin, 3

Walknstein, 4
Walpole, Horace, 3
Welsh, William, 4
Wesley, John, 3
Widal, 4
Wilson's tincture, 4
Wolsey, 4
von Wurthenberg, Herzog, Christian, 3

Xanthine, 168
X ray findings, 69, 128, 163
  acute gout, 69, 128
  ankylosis, 63, 70
  calcium deposition, 63, 73
  chronic tophaceous gout, 162
  differential diagnosis, 134, 142

Zinzendorff, Cardinal, 4